BRAIN

VOL. 84, PART 2.

THE NEUROLOGY OF LANGUAGE[1]

BY

RUSSELL BRAIN

INTRODUCTION

THIS year happens to be a triple centenary, for in 1861 Hughlings Jackson (Hutchinson and Jackson, 1861) published his first paper, Henry Head was born, and on April 18 Broca (1861) reported to a meeting of the Anthropological Society of Paris his aphasic patient who was to have such a profound and lasting influence on thought about aphasia. It seems to me appropriate, therefore, to commemorate in this lecture not only Hughlings Jackson, but also his two contemporaries, and particularly Henry Head. Today when discussing the neurology of language it is difficult to dissociate Jackson and Head. Head's thought was entirely Jacksonian in spirit, and he repaid the debt by making Jackson's views more widely known and developing and extending them.

We may note in passing how very slender today seems the anatomical basis for Broca's ideas, for the patient from whom he inferred that the lesion of the frontal lobe was responsible for the loss of speech, had a softening of the left cerebral hemisphere which not only involved the greater part of the frontal lobe but produced a cavity the size of a hen's egg, which extended backwards as far as the ascending parietal convolution, below to "the marginal convolution" of the temporosphenoidal lobe, and in its depth involved the insula and "the extraventricular nucleus of the corpus striatum."

It may be said, with some truth, that the correct theoretical interpretation of aphasia is of little clinical importance, and will not make it any easier to localize a cerebral lesion. Both Jackson and Head, however, saw its wider implications. Since speech is a distinctively human characteristic, when we study its organization in the nervous system we are looking at something which is of the essence of human nature, and of the relationship between the brain and the mind. Moreover, we cannot consider the

[1] Based upon the Hughlings Jackson Lecture, delivered at the Royal Society of Medicine, London, February 16, 1961.

XUM

effects of brain lesions upon language without encountering the general problem of cerebral representation and localization. At two points, therefore, the neurology of language touches fundamental problems of neurology.

The first seven chapters of the first volume of Henry Head's (1926) "Aphasia" are a critical review of the subject up to the time at which he was writing. The sixth is entitled "Chaos", and if Head could have foreseen the conflicting views still being expressed about aphasia today, he would hardly have found the situation more orderly than it was then. I shall not spend time reviewing past ideas in any detail, but before I come to the present, and the future, I want to consider briefly what seems to me to be the cause of the chaos, why it is possible for workers in this field still to have such conflicting views, and why no current interpretation of aphasia seems entirely satisfactory. This, I suggest, springs from the nature of speech, which functionally must be considered both psychologically and physiologically. As Jackson (1878*a*) put it, "speech and words are psychical terms; words have, of course, anatomical substrata or bases as other psychical states have. We must as carefully distinguish betwixt words and their physical bases as we do betwixt colour and its physical basis; a psychical state is always accompanied by a physical state, but nevertheless the two things have distinct natures."

The most elementary unit of speech is the phoneme, each of which is a particular kind of speech sound, and since printed letters may be sounded in different ways there are more phonemes than letters in the alphabet, and they have distinctive symbols in phonetics. A phoneme, however, is an abstract idea, for each person pronounces the same phoneme in a different way from everyone else. So we have to give a different name to the actual sounds produced in speech—phones, and say that a phoneme is a category of sounds which embraces all sufficiently similar phones (Brown, 1956). Both phones, which are sounds, and phonemes, which are categories of sounds, are psychological entities. So, of course, are groupings of phonemes into words, and words into sentences, and names and meanings. And, when speech breaks down in aphasia, this breakdown presents itself in the form of a psychological disorder. When we say that the patient cannot say what he means, or understand what he hears, we are using psychological terms to describe what is wrong.

The Relationship between Anatomy, Physiology and Psychology

Aphasia then is a psychological disorder, but it presents itself to the clinician as a symptom of an anatomical lesion, usually focal. What is the relationship between them?

Historically it is possible to recognize three main schools of thought on this question.

(1) The first view is the naïve psychoanatomical. In the broadest

sense we all aim at a psychoanatomical account of psychological activities, that is at establishing the most detailed possible correlation between the mind and the brain. The naïve psychoanatomical view, however, assumes that there is a direct relationship between psychological functions and localized areas of the brain. It follows from this that localized lesions of the brain can and do produce limited defects, which correspond to psychological functions. There have been many exponents of this view from Bastian (1898) in the early days through Henschen (1920, 1922) in an intermediate period up to Kleist (1959) at the present day. But I will illustrate it by quoting Charcot (1887) whose views on aphasia are perhaps a little less familiar. Charcot said that a word is a complex composed of four fundamental elements, an auditory image, a visual image, and two motor images, one articulatory and the other graphic. There may be an amnesia for any of these or for a combination of them and therefore "it follows that the various groups of memories have their seat in certain localized regions of the brain." Here then are words analysed into supposed psychological factors—remembered images, each variety of which is naïvely regarded as localized in a particular anatomical region of the brain. The best way to recognize the defects of this kind of approach will be to see what is involved in a more satisfactory one, but Hughlings Jackson implicitly criticized the naïve psychoanatomists when he said in a continuation of the passage quoted above: "We must not say that the 'memory of words' is a function of any part of the nervous system, for function is a physiological term," and "a method which is founded on classifications which are partly anatomical and physiological, partly psychological, confuses the real issues" (Jackson 1878*b*).

(2) In contrast to the naïve psychoanatomical view there are the clinical psychologists. Their interest is concentrated on the description of the psychological disturbance of function in aphasia, while the relationship of this to anatomy is largely neglected, or a vaguely holistic view is proposed. We owe a double debt to the many workers, ultimately disciples of Jackson and Head, who belong to this school—a negative one, for all that they have done to expose the inadequacies of the naïve psychoanatomists, and a positive one, for preparing the ground for a psychological interpretation which is now beginning to yield a rich harvest. But they have done little to advance our knowledge of the fundamental problem of the relationship between the mind and the brain in the sphere of speech. Goldstein (1948), for example, who owes much to Jackson and has added a great deal to our understanding of aphasia as a psychological disturbance, when it comes to anatomy writes: "The symptoms which are related to a localized lesion . . . cannot be understood simply as due to memory defects; they are consequences of a diminution of function of the brain matter, which finds its expression in a dedifferentiation of performance . . . Our discussion will have shown that as much as the rejection of the old concept of circumscribed

localization is justified, such a rejection is not in contradiction to an assumption that to each performance corresponds an excitation of definite structure in the cortex, indeed, not in a circumscribed area but widespread over the whole cortex, differently in each performance. This is what we should term localization."

Head (1926) himself well illustrates the dilemma in which the clinical psychologist finds himself. His classification of the aphasias was psychological, for he recognized four groups characterized predominantly by defective word formation, defective syntax, defective naming and defective comprehension of the significance of words and phrases as a whole—all psychological disorders. But when he comes to cerebral localization he becomes involuntarily a naïve psycho-anatomist, for he says: "On this high level the problem of 'cerebral localization' acquires a somewhat different aspect and is greatly increased in complexity . . . We must first distinguish categorically the various defects in the use of language and then attempt as far as possible to determine their relation to the locality of the lesion in the left hemisphere." And then: "there are no 'centres' for speaking, reading, writing or other forms of behaviour comprised in the normal use of languages," but "if the lesion falls over the lower portion of the central convolutions and the parts beneath them, the patient has difficulty in finding verbal forms in which to express his thoughts. Injury to the temporal lobe, on the other hand, leads to disordered rhythm and want of grammatical structure; speech tends to become true jargon. A lesion lying between the post-central fissure and the occipital lobule disturbs the appreciation of meaning, either verbal or general. Should the destruction occupy the neighbourhood of the angular gyrus, it is mainly the nominal value of words which suffers. If, on the other hand, it lies in the region of the supramarginal gyrus, the patient finds difficulty in recognizing the ultimate significance of logical conceptions evolved by himself, or placed before him orally, in print or in pictures." Here in spite of all his protestations against "the diagram-makers" he correlates each loss of a specific psychological function with a localized anatomical lesion.

(3) The third historical school of thought on aphasia may be described as the empiricist. This abandons the attempts to *interpret* the relationship between the psychological disorder present in aphasia and the anatomical situation of the lesion. It is content to say that certain forms of aphasia can be recognized *clinically* by the disorders of function which characterize them. Members of this school may differ about the number of distinct forms which they recognize but they are apt to agree that recognizable forms tend to merge into one another. To emphasize their empiricism they are likely to describe the varieties of aphasia eponymously as, for example, Broca's aphasia or Wernicke's aphasia, in order to avoid any suggestion of a psychological interpretation. Even the empiricist school, however, does not escape all difficulties, more particularly when it comes

to localization, for although there exists a rough relationship between a particular clinical variety of aphasia and a lesion in a certain situation in the brain, exceptions to these correlations are notorious, and are well illustrated by Conrad's (1954) observations on the wide scatter of the lesions responsible for Broca's aphasia and pure word-dumbness (figs. 1 and 2).

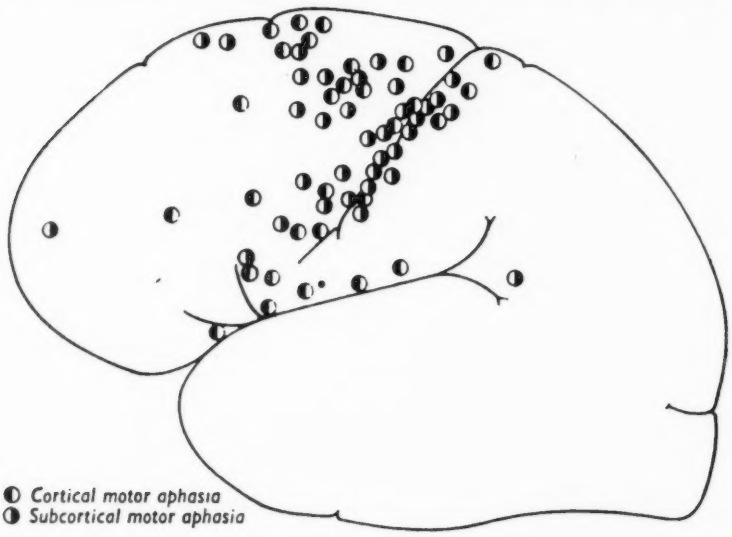


FIG. 1.—General view of all cases of motor aphasia in Conrad's (1954) series of fractures of the skull. The circles indicate the middle points of the trephine defects.

Most students of aphasia can be classified in one or other of these three schools, none of which, however, provides a very stable position. Hybrid descriptions are common, such as 'subcortical motor aphasia', which is a blend of anatomical, physiological and psychological concepts. Physiological terms, such as motor and sensory, occur in the literature from time to time, but historically at least scarcely justify the recognition of a physiological school of thought.

I suggest that the source of all this confusion is the failure to recognize that speech involves a three-term relationship, or a description at three levels, and an understanding of the relationship between them: these are the psychological, and physiological, and the anatomical. An anatomical lesion of the brain, if it disturbs speech, does so by disorganizing the physiological functions upon which speech depends. This leads to an associated psychological disorder. If we try to interpret the neurology of speech solely by means of observations made on aphasic patients, we are hampered by having to deal with two unknowns—the relationship of

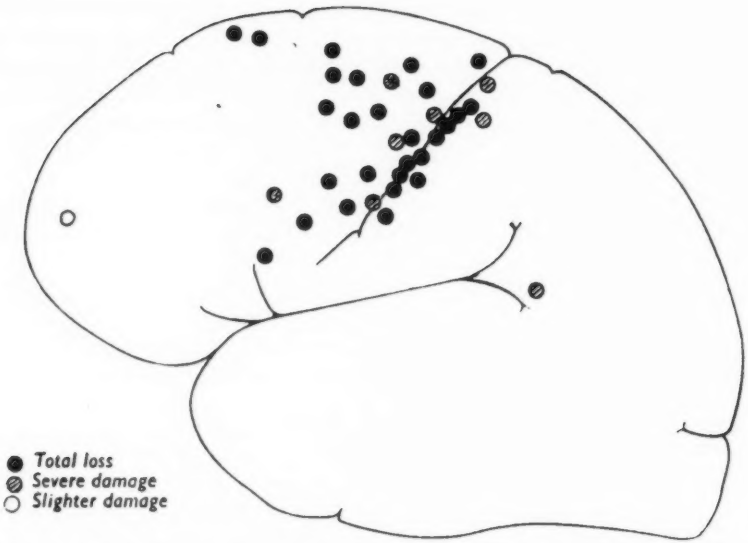


FIG. 2.—Cases of subcortical motor aphasia (according to the terminology of Wernicke). The symbols show the degree of speech disturbance immediately after the lesion (Conrad, 1954). Note in both figures the distribution of the lesions in the superior frontal region in the neighbourhood of Penfield and Roberts' "supplementary motor area." (Figs. 1 and 2 published by permission of Dr. Conrad.)

psychological and physiological function, and the relationship of physiological function to anatomical structure. Physiology is concerned with dynamic processes of extreme complexity extending over wide areas of the nervous system, and always involving time as a factor in their description: we can hardly expect to learn much about them by studying the psychological effects of chance focal anatomical lesions. Moreover, studies of the neurology of language based solely upon aphasia seem exposed to the logical difficulty that if we begin by inferring the normal from the pathological, we cannot then use it to explain the pathological. On the other hand, if we can establish some independent basis for the physiology of language, we can use that to interpret aphasia, and the study of aphasia to enlarge and enrich it.

Though animals can communicate with each other in a limited fashion, speech is peculiar to man, hence the ordinary methods of experimental animal physiology can throw no light on it, and the observations of this kind which it has been possible to make upon human beings have been very limited. Nevertheless, by using several converging methods it is possible to infer a good deal about the physiological organization of human speech. All of these methods, moreover, are of a kind which is extensively

used in animal physiology, namely, the observation of the responses to stimuli. But since speech is a psychological as well as a physiological process, the responses will often be psychological as well as physiological, and indeed it is only from observations on both that we can hope to correlate them. The extent to which the observations are measurable varies. As we shall see, some modern methods of speech investigation employ methods which yield results which are measurable to a high degree of accuracy, and capable of mathematical treatment.

The Development of Speech in Infancy

The first source of information about the psychophysiology of speech is the study of the development of speech in infancy, about the course of which there is general agreement. I need now draw attention only to certain features. The third stage of infant vocalization is *babbling*, which usually begins towards the end of the second month. The fact that the normal child hears the sound which it produces is of great importance for the further development of its speech. Children born deaf begin to babble, but soon cease to do so. Bühler (1930) says, "the psychologically important fact is the formation of strong associations between the auditory impression and the movements which produce it, for this is the essential basis of the later imitation of the sounds the child hears, in which it has to translate what it has heard into vocal movements of its own." As Froment (1935) well puts it, "it is by trial and error guided by the ear that the baby learns all articulatory processes." He compares it with a violinist tuning his instrument. We are familiar enough with the general importance of afferent impulses from muscles for the regulation of movement: speech is influenced by auditory impulses as well, and both are produced by its motor element. Thus at this early stage, and hence fundamentally, speech is a sensorimotor-sensory activity but, whereas congenital deafness interferes grossly with the development of speech, when once normal speech has been established acquired deafness disturbs it relatively little. Observations have recently been made on the effects of artificial disturbances of what has been termed "the auditory feedback" (Lee, 1950; Black, 1951). If a person's own speech is played back to him after a short delay through closely-fitting headphones, his rate of speaking becomes slowed, and other disturbances appear. There is more than one possible explanation of this.

But, to return to the developing child, Eisenson (1938) points out that after it has learned to imitate many sound combinations of its own accidental making, it has laid the foundations for the next step to the development of speech, *echolalia*. This is the imitation by the child of sounds which it hears others make, but which it does not itself understand, and this stage of speech begins at about the ninth or tenth month. As Eisenson says, during this stage, "the child acquires a repertoire of sound complexes which ultimately he will come to be able to produce at will, and which he

XUM

must have before he can learn to speak, or acquire a language, in the adult sense."

But echolalia is a highly complex process. We say that the child imitates sounds made by others, but what we call *the same sound* made for example by its father and its mother, though they may both be the same phoneme, are composed of phones which differ in pitch as well as in other characteristics, and which therefore constitute very different physical stimuli; and the sound which the infant makes, if it successfully imitates them, is a sound yet again of a different pitch, which must therefore sound different to the child itself. Already at this early stage of speech development, therefore, the child is learning to recognize and reproduce the phoneme—a pattern which is common to the sounds made by its parents and by itself, although in other important respects these sounds differ from each other. We need not now consider the probably complex process of learning which leads to this result: in physiological terms it means that a wide range of stimuli becomes capable, in virtue of some factor common to all of them, of arousing a sterotyped motor response.

Echolalia prepares the way for and merges into the final stage in the development of speech by the child, which is *verbal utterance*—a stage which is itself long and complex and which I cannot now discuss in detail: I will draw attention only to certain important features. A number of writers have pointed out that the child begins by using single words, which often have a strong emotional colouring, and which express the child's emotional attitude towards the word, and the experience for which it stands. The phonetic and intonational characteristics of the word therefore may vary independently. The objective reference of a word is often very different from that of the same word used by an adult, and when a word is used for naming, it is often wrongly extended from one subject to others which are not really of the same kind. At first the child's imitation of sounds made by adults in uttering words is defective, and Lewis (1936) compares its errors with those of an aphasic. Speech shows distortions, transpositions, and reduplications, and at this stage the child understands much more than it can say. Naming is the essence of the symbolic function of speech: it depends upon the association of the word with the object to which it refers, which implies increasing accuracy in recognizing and abstracting from the environment the precise element for which the name stands. Beginning with concrete objects and persons, naming becomes increasingly abstract as it refers to qualities, actions, relationships, and ultimately highly abstract ideas. Thus, physiologically, naming involves superimposing upon the sensorimotor organization of speech, already being established, a physiological link between this and the physiological basis of the recognition, at first of objects, later of images or ideas representing objects or their qualities, actions, or relationships. As speech develops, and words are used in combination, grammar and syntax link them together, and their mutual

modifications and temporal order in sentences make it possible to express more and more complex meanings.

The Physiology of Phonetics

Another method of investigating the psychophysiology of speech has sprung from the impetus which the development of electronics has given to communication theory and practice. Electrical methods of recording have made it possible to analyse in great detail the physical characteristics of the sounds of which speech is composed, to synthesize them individually, and unite them at will, to vary their physical features, and, in what are known as articulation tests, to investigate the effect of these variations upon the auditory recognition of speech sounds and words. In this growing field of new knowledge I can pick out only a few salient features. The cardinal question is, since the same phoneme, or speech sound, can be produced in an unlimited number of ways, depending upon the pitch of the voice, the resonance of the vocal organs, etc., by what means do we recognize all these variants as identical? This question has proved very difficult to answer. From numerous experiments it has been concluded that "the

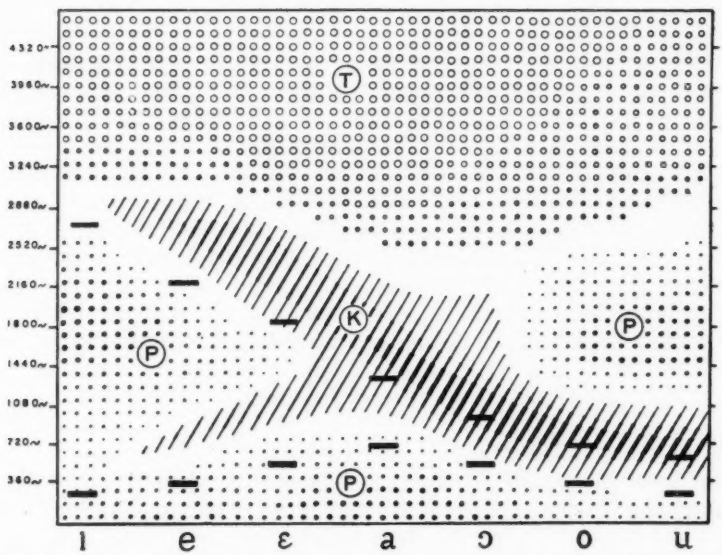


FIG. 3.—Schematized figure of the unvoiced stop consonant produced from spectogram and varied in position on frequency scale (ordinates) before each of the seven cardinal vowels (abscissae). The figure shows the effect of these variables upon the auditory identification of the stop consonant as p, t, or k. (Liberman, Delattre and Cooper, 1952.) (Published by permission of the editor of the *American Journal of Psychology*.)

XUM

listener does not seem to depend upon amplitude alone, nor upon frequency or time alone. The fundamental acoustic determinant of his response is the distribution of energy at different frequencies as a function of time: the intensity-frequency-time pattern" (Licklider and Miller, 1951). Liberman, Delattre and Cooper (1952) artificially produced a single unvoiced stop consonant at twelve different frequencies and placed it before each of seven vowels. They demonstrated that the subject might hear the consonant as either k, p, or t, depending on frequency and the vowel by which it was followed (fig. 3), hence what consonant is heard depends not only on the physical stimulus representing the consonant, but also on which vowel follows it, from which they conclude that the following vowel "plays a critical part in the auditory perception of p and k," and "in that event the irreducible correlate for p and k is the sound pattern corresponding to the consonant-vowel syllable." Everyday experience of visual symbols shows the same thing: in reading, the sound which reproduces the letter t is different according to whether it is followed by a vowel or by h.

This leads naturally to the fact that a word is perceived as a whole, which is something different from the mere sum of its parts. This, of course, has long been familiar in all forms of language. It is illustrated by the general principle that in a given time a much larger number of units of speech, whether they be heard phonemes or printed letters, can be recognized if they are presented as words than as nonsense syllables, or as sentences than as isolated words (Egan, 1948). Similarly it has been shown that if telegraphists are tested with a strange code or list of figures, they are able to receive only three or four units, compared with forty to sixty in the same time if they are presented with morse code arranged in words which make sense (Bryan and Harter, 1897, 1899). The same thing may be observed in the breakdown of speech in aphasia; for example, a patient with alexia may be able to read an individual word, though he cannot read the letters of which it is composed. All these observations point to the fact that physiologically a word is an organization of a higher order than the units of which it is constructed, and that the organization of these units which follow one another in time actually modifies the perception of the units themselves —an idea closely related to the Gestalt approach of Conrad (1954).

Factors Which Determine Meaning

Just as a word is an organization of a higher order than the phoneme, so a sentence is an organization of a higher order than a word. And like a word, a sentence is an organization, which takes time to come into existence, and in which what happens later modifies the significance of what happens earlier, so that the earlier parts must be held, as it were in suspense, until the later parts determine their meaning. The most obvious example of this is provided by homophones, that is words which sound the same but have different meanings. For example, if I begin a sentence with the

words "The right . . . ," you do not at that stage know what the word "right" means. I might be going to continue, "The right way to classify aphasia . . . ," in which case the meaning of right would be "correct," or, "The right cerebral hemisphere . . . ", in which case the meaning of the word "right" would be "opposite to left," Thus the meaning of the word "right" is in a state of suspense until it is determined by words which are heard later. Meaning, therefore, depends upon verbal or syntactical context.

Words derive their meaning also from another kind of context which I propose to call the context of interest—a term which includes attention to an object in the environment, or an idea, together with the feelings and intentions of the speaker and hearer with regard to it. Some words obviously have meaning only in relation to the external environment—the word "that" in "Give me that," for example, is meaningless unless both speaker and hearer can see what "that" refers to. But here is a perhaps less obvious example. Consider the five words, "Will you take the chair?" What this sentence means can be decided only in relation to the context. It might mean, "Will you preside at the meeting?" or, "Will you sit on the only chair in the room?" or, "Will you remove the chair—with the table?" or, "Will you accept the professorial appointment?" In the second and third examples the meaning of "take the chair" is determined by the actual physical environment, as well as by the intentions of those present. In the first and fourth instances the meaning is independent of the physical environment, for the conversation might take place anywhere: it derives from the past experiences, present relationships and future intentions of the speakers. And not only does the context of interest determine the meaning of the word "chair," but this in turn determines the meaning of the word "take," which in the four sentences means, part of preside, or sit on, or remove, or accept. These are psychological facts, but they imply physiological correlates. In other words, at the physiological level, the fact that the context determines the meaning of a word implies that the physiological basis of perception is linked with that of speech when the context is chiefly the external environment. When it is the context of interest—a subjective state, which gives meaning to words, the physiological basis of perception is replaced by those of images, memories, or ideas. The importance of environment in relation to meaning is illustrated in aphasia when a patient succeeds in naming objects in their normal environment which he cannot name if they are presented to him artificially as part of a test.

The Physiology of Speech

We are now in a position to look in more detail at the physiological problems which speech presents. To go back to the beginnings of speech in the infant, we have seen that this is based upon a sensorimotor-sensory circuit, by means of which the child reproduces the sounds which it hears

XUM

and regulates its own motor activity in doing so. We saw also that the child hears what we call *the same sound* produced in many different ways by different people, whereas its own production of this sound is relatively stereotyped. Physiologically, therefore, the first problem is how these widely varying stimuli can produce the same response, that is, by what physiological mechanism the brain responds to a common pattern in the stimuli, and disregards the irrelevant elements.

Liberman, Delattre and Cooper (1952) suggest that, in their experiments described above, what determines whether the unvoiced stop consonant shall be heard as p or k is "the articulatory movements which the listener would make in attempting to reproduce these acoustic patterns, or perhaps only the short-circuited neural equivalent of these movements, with the result that the initial schematic phonemes p and k which can be entirely identical as acoustic stimuli become clearly differentiated in proprioceptive terms and are therefore finally perceived as distinctively different words." They claim that the observations provide "some additional support for the assumption that the perception of speech depends in any final analysis on the proprioceptive stimuli which arise from the movements of articulation." This hypothesis also affords support to the idea that there is a basic element in speech perception which is sensorimotor, rather than purely sensory, but it does not solve the problem of how the phonetic pattern is discriminated. Bergson (1896) in his too little known observations on aphasia explicitly stated this problem, and said that we speak of the auditory image of a word as if it were an entity or a category, but it could be this only for "a memory which schematizes the resemblance of complex sounds." Unaware then of Bergson's ideas, I introduced the concept of the schema (Brain, 1950) for this purpose, borrowing it from Head and Holmes (1920), though I use it in a somewhat different sense. Head and Holmes introduced the word "schema" to describe an unconscious physiological record of the body posture as a standard against which a change of posture could be compared. The schema, as I use it in connexion with speech, is an unconscious physiological standard of comparison, but, unlike the body schema of Head and Holmes, most speech schemas, when established, remain stable parts of the permanent equipment of the individual. Thus the physiological basis of the recognition of a phoneme, i.e. of the basic element of speech, is an auditory phoneme-schema. However, a phoneme may be uttered, we identify it at once without any process of conscious comparison with a standard: the schema is therefore purely physiological.

But phonemes exist only as constituents of words. We have already seen that when two phonemes occur consecutively the second one may influence the way in which the first is perceived. Thus when phonemes are linked together to constitute a word, this process is more than a simple addition: a word constitutes a unity or pattern at a higher level of organization.

Hence, just as the recognition of a phoneme depends physiologically upon the existence of the appropriate phoneme-schema, so there exist word-schemas which play the same part in the recognition of words.

These ideas closely correspond to those of Conrad (1954), who distinguishes two phases in the understanding of speech in terms of the Gestalt theory. "In the first phase," he writes, "the auditory formation of speech has to be grasped purely auditorily, and to be detached from its auditory background without understanding having necessarily taken place at this stage. The individual must be capable of detaching the auditory Gestalt as such, clearly and sharply defined, final and constant in its whole structure . . . In the second phase it is necessary to understand the auditory Gestalt as conveying meaning."

We can distinguish two further physiological processes which must play a part in the comprehension of spoken speech. Both are concerned with the meaning of words. That a word exists independently of its meaning is obvious from the facts that a child can learn a word, and adults the words of a foreign language, without knowing what they mean. Their meaning depends, first, on their power to refer to something in the surroundings or to evoke the appropriate ideas. Hence, a word-schema must possess links with the physiological bases of perception and thought. Secondly, the meaning of words depends upon the relationship of each individual word to those which precede or follow it in a sentence, that is upon syntax.

This raises the difficult problem of serial order (Lashley, 1951). A sentence is a series of words which follow one another in time, and is subject to laws whereby the meaning of the earlier words may modify or be modified by the later ones. This implies that the physiological activity excited by the earlier word-schemas is a continuing one and also capable of modifying or being modified by later ones. The capacity of the nervous system to hold in suspense a number of linguistic units is well illustrated by the work of telegraphists (Bryan and Harter, 1897, 1899). An expert telegraphist, when receiving morse, does not immediately transcribe what he receives: he prefers to keep from six to twelve words behind the message he is receiving before he begins to transcribe it. The unit of the morse code is a click, and experiments have shown that such a telegraphist at any moment is storing on the average 237 clicks in their correct time-relationships before he begins to transcribe, and, of course, while he is transcribing those he is receiving a further series. Thus on the receptive side a long succession of stimuli is converted for storage into a persistent or simultaneous state. The reverse happens when an idea is put into words: then we begin with the idea which exists entire at a specific moment, but finds expression by evoking words in a serial order mutually modified by grammar and syntax. These two factors in meaning, which we may call the syntactical and the semantic, must be very intimately related at the physiological level, because both the serial order of words and their

XUM

syntactical relationships influence their meaning, and, conversely, meaning is reflected in serial order and syntax.

Since I am concerned mainly with principles, I shall not now develop the application of the concept of the schema to the motor organization of speech, though I shall allude to this when I come back to aphasia.

The Mode of Action of the Schema

By what physiological organization, to take the simplest instance, does an auditory phoneme-schema respond to the common pattern in an indefinitely large range of otherwise dissimilar groupings of phones, that is, sounds? This is only one example of a more general question which is a fundamental one in neurology, namely, the physiological basis of the recognition of patterns, which is an integral part of perceptual recognition. To put the question in another way, how can a large number of variable stimuli elicit the same stereotyped response? Various hypotheses have been put forward in explanation of this, and at the moment they can be no more than hypotheses. If, however, we can formulate a hypothetical principle which will explain the facts, we can then ask the neurophysiologist whether the structure, and the functions, of the nervous system are capable of acting in accordance with the hypothesis and whether there is any evidence that they do. If we may regard the schema as a kind of receptor, there cannot be a one-to-one correspondence between the stimulus and the receptor, for in such a case only one particular stimulus would be capable of exciting the response. What we have is a receptor which is capable of detecting, and responding to, *a pattern* in varying stimuli, that is, discovering what set of properties of the stimulus is essential for it to be of a given class. I suggest that most of the features which underlie the recognition of a pattern can be explained at their various stages as the result of *calculating the probability* that a stimulus possesses a certain set of properties. Regarding speech, consider first the recognition of a phoneme. A large number of phonetic variants, as we have seen, are recognized as the same phoneme. Beyond this range of acceptable phonetic patterns there are others which are recognized only with difficulty, or not at all, or present themselves to consciousness as different phonemes. This can be expressed by saying that for all these variants there is a critical probability which decides whether they are, or are not, identified with the phoneme in question. Fletcher (1953) says that "articulation values may be considered as probabilities," and gives examples of this. The same is true of the reading of handwriting. When we read handwriting which deviates from the normal, what we are doing unconsciously is estimating the probability that a particular pattern represents a particular letter. Beyond a certain point this becomes so improbable that we fail to recognize the letter. There is a critical probability influenced by our memory of previous examples of the handwriting.

Both in the spoken and the written word our interpretation of a particular phoneme or letter is influenced by the other phonemes or letters in the word. Vowel sounds differ greatly in different parts of the country, but in spite of these deviations we often recognize the phoneme they stand for because of their relationship with neighbouring consonants: in other words, these influence the probability upon which the recognition of the vowel phoneme depends. The same principle of the influence of context applies in syntax, when, for example, the meaning of a word is influenced by words uttered later in a sentence. Till the later words are uttered, the earlier word may have several meanings, that is, the probability of any particular meaning is too low to be capable of evoking it. The later words when they appear raise the probability that the first word has a particular meaning above the critical level.

Two experts in information theory, MacKay (1956) and Uttley (1956, 1958), have used the probability theory, though in slightly different ways, to explain the capacity of the nervous system to react in a stereotyped fashion to a wide range of varying stimuli. Sholl and Uttley (1953) have proposed a theory of pattern discrimination in which matching consists of an estimate of the probabilities of a collection of variables corresponding to a model built up by previous experience, and they and Sholl (1953) suggest that the organization of neurons in the cortex may fulfil the conditions necessary for this hypothesis to work. Further observations by Sholl (1959) again suggest that the arrangement of cells in the cerebral cortex is such that "the physiological basis of pattern recognition can only be specified in statistical terms and by probability laws."

Thus, although we are only at the beginning of an understanding of these questions, we can see the outlines of a correlation between a psychological and a physiological interpretation of the processes which underlie speech, and that it may be possible to correlate both with the minute structure and functional activity of the cerebral cortex; and we can also see broadly the directions in which we must look for verification of these hypotheses.

The Anatomy of Speech

If we are to escape the mistakes of the naïve psychoanatomists, our aim must be to correlate the physiology of speech with its anatomy, and not try to jump straight from psychological function to anatomical structure. The correlation of the physiology with the anatomy is difficult. We know a good deal about the cortical representation of hearing and vision, and rather less about the cerebral organization underlying the simple movements of speech and writing, for there is still much that is obscure about the physiology of movement in general. Concerning the location of the physiological links between the receptors and effectors in speech, we know very little, chiefly because practically our only information about this is

derived from the effects of pathological lesions, and there has hitherto been no adequate physiology in the light of which to interpret them. I shall therefore leave this aspect of the question till my next and final section, in which I discuss aphasia once again. Meanwhile, there are two new aspects of the anatomy and physiology of speech to which I want to draw attention. The only observations on man which can be regarded as using methods in any way equivalent to those of experimental physiology are based upon stimulation of the brain of the conscious patient in the course of operations, and surgical excisions of localized areas. Penfield and Roberts (1959) have reported that such electrical stimulation may produce either a positive effect—stimulation—or a negative one—interference. The positive effect, which is never more than a cry—vocalization—can be produced by electrical stimulation of the Rolandic and supplementary motor areas of either hemisphere. Stimulation of these areas may also interfere with speech, and interference may be produced by application of the current to the left Broca's and posterior temporo-parietal areas in a right-handed person, and rarely to similar areas of the right hemisphere when that is dominant. Thus from bilaterally situated motor areas it is possible for electrical stimulation to evoke vocalization, or to suppress speech, while from the so-called "speech areas" only suppression of speech can be elicited. Penfield and Robert's observations were limited to the suppression of spoken speech: they do not seem to have observed the temporary abolition of the comprehension of speech. Both occurred spontaneously in a patient Dr. J. D. Spillane has kindly allowed me to mention. This was a man with a left temporal lobe abscess who had two brief attacks of aphasia while he was having an EEG. In the former he was unable to speak, but could understand what was said to him, and this attack coincided with a brief dysrhythmic episode in the left fronto-temporal area. In the second attack he could speak but not understand what was said to him, and the dysrhythmia was in the posterior temporal region (fig. 4). Penfield and Roberts state that the entire supplementary motor area has been excised without permanent aphasia. On the other hand, temporary but sometimes prolonged aphasia may follow removal of the supplementary motor area of the dominant hemisphere. We need more clinical observations on the effects upon speech of lesions on the medial aspects of the hemispheres (but see figs. 1 and 2).

Aphasia has sometimes been observed to result from stereotaxic operations on the globus pallidus or optic thalamus for the relief of Parkinsonism. This may be an accidental remote effect, perhaps of a disturbance of the circulation in other areas of the brain already recognized as being concerned with speech. There is, however, a possibility that the corpus striatum is more directly concerned in speech than has hitherto been suspected, perhaps through its corticothalamic and thalamocortical connexions. Further observations are needed on this point.

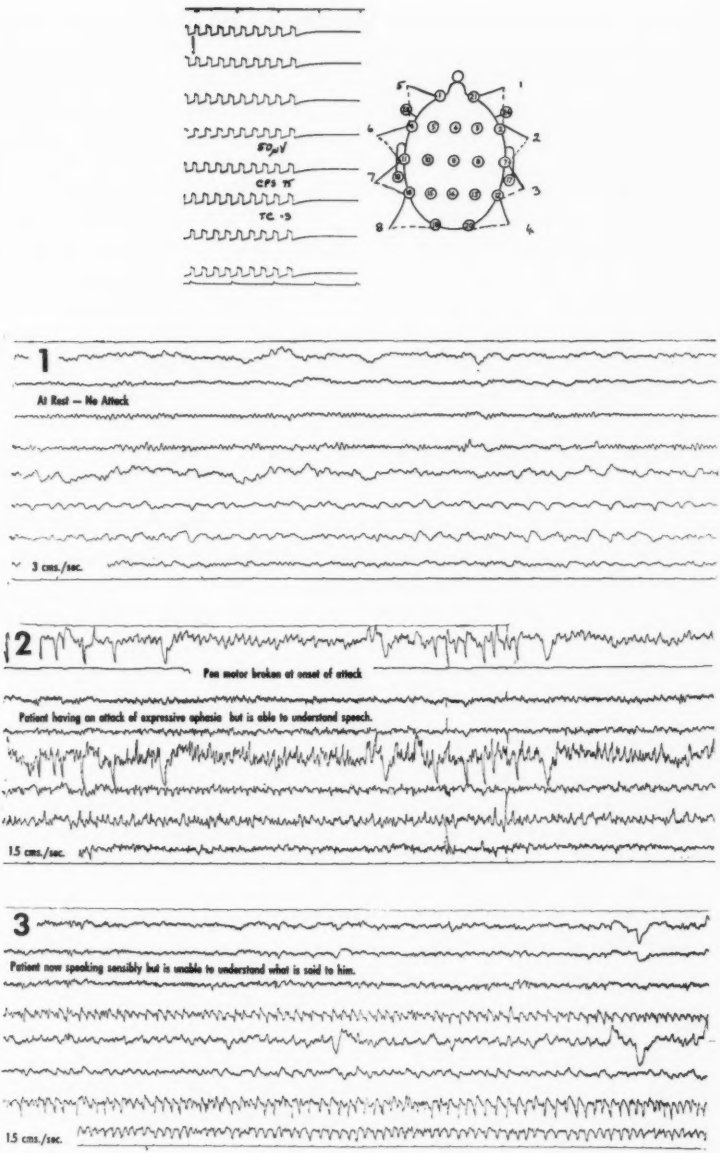

50 μV
CPS 7
TC .3
1
At Rest — No Attack
3 cms./sec.
2
Pen motor broken at onset of attack
Patient having an attack of expressive aphasia but is able to understand speech.
1.5 cms./sec.
3
Patient now speaking sensibly but is unable to understand what is said to him.
1.5 cms./sec.

FIG. 4.—Patient with left temporal abscess. Electroencephalogram (1) at rest, (2) during attack in which he could understand speech but not speak, (3) during an attack in which he could speak but not understand speech. In (2) the dysrhythmia is chiefly recorded on lead 5; in (3) on leads 7 and 8. (Kindly lent by Dr. J. D. Spillane.)

XUM

The Physiology and Psychology of Aphasia

To sum up our conclusions so far, we may say that speech employs a series of complex physiological organizations which I have termed schemas, and of which we may recognize in relation to spoken speech (1) auditory phoneme-schemas, (2) central word-schemas, (3) word-meaning schemas, (4) sentence schemas, and (5) motor phoneme-schemas. To serve the purpose of reading and writing, additional visual and graphic schemas are superimposed upon the fundamental schemas of speech, and there is evidence that calculation, musical appreciation and execution, and possibly other skills, have their own independent schematic organizations. If the various schemas enumerated represent individual physiological functions, we should be able to detect in aphasia evidence of their disorganization. But since aphasia is usually the result of a focal anatomical lesion, there will be varieties of aphasia corresponding to disorganization of specific schemas only if each type of speech schema is organized anatomically in isolation from the others, for only then can we expect focal anatomical lesions, if they are not too large, to damage individual physiological organizations.

What type of speech disturbance should we expect to result from a disorder of each particular kind of schema? Since the central word-schema is the basic element in both the comprehension and the expression of words, a disorganization of this will lead to a disturbance of the understanding of words as such, whether they be spoken or written, and also of their phonemic structure and use in expression, again whether spoken or written (i.e. paraphasia and paragraphia). The power of the words to evoke and express meanings will be defective because the words as psychophysiological units are defective.

Word-meaning schemas represent a higher level of physiological organization than central word-schemas. When word-meaning schemas are disorganized the patient will have plenty of words available and will often be able to read and write them correctly, but their power to evoke and express meanings being disturbed, he will not be able to understand much of what he hears and reads, and will have great difficulty in expressing meanings in uttered speech and in writing. This type of disorder may, in milder cases, chiefly affect the nouns, when there is difficulty in thinking of the names of things. In more severe cases when the meanings of verbs and relational words is impaired, speech is more severely affected both in comprehension and expression. When word-sentence schemas are disorganized the patient will show that though he knows the meaning of the individual words, the meaning of the sentence as a whole, created by their syntactical relationships, escapes him.

The aphasic patient is a person with a lesion which, according to its size and situation, is disturbing one or more of the physiological organizations concerned in speech. Only rarely do we find a single type of schema

affected alone. In respect of spoken speech, I believe this occurs only with small lesions near the auditory receptor area in the dominant hemisphere, and in relation to the most distal motor functions. The former leads to so-called word-deafness, which physiologically I regard as due to a disorder of auditory phoneme-schemas. The corresponding motor disorder is pure word-dumbness, a disorder of motor phoneme-schemas, and here the evidence for the association of this symptom with a consistently localized anatomical lesion is much less definite. In either case, it is possible that the degree of damage is more important than its precise localization. Corresponding to these peripheral disorders in spoken speech are pure word-blindness, and the rare disorder, pure motor agraphia, in the sphere of reading and writing. Whether one terms all these conditions varieties of aphasia or varieties of agnosia and apraxia is, I think, purely a matter of definition.

When we come to the effect of brain lesions upon central word-schemas, word-meaning schemas and sentence-schemas, the situation becomes extremely complex, and will require more work for its elucidation. There are two reasons for this. Since all the evidence indicates that the anatomical basis of these physiological functions is situated in a comparatively limited area of the temporal lobe and the adjacent parietal lobe in the dominant hemisphere, and since the lesions which produce aphasia tend to be large, every possible degree of disorder of these specific functions may exist in combination, not only with each other but also with pure word-deafness. The second reason is that disorders of different physiological functions may produce similar psychological defects. Thus, if there is a disorder of central word-schemas, since the accurate use of words is essential to syntax, syntax also will be disturbed, but so it will too if the central word-schemas are intact but their ability to elicit meanings is disordered, or again if the syntactical use of words, that is, their serial order and resulting modifications, is disorganized. Owing to the complex functional interrelationships between the different types of schema, then, we cannot directly correlate what we describe as a single psychological disorder, such as defective syntax, with a single kind of physiological breakdown, as Bay (1957*c*) has pointed out. Schuell (1950) makes the same point in relation to paraphasia, which, he says, is not simple or single in ætiology but may indicate a breakdown at various "pre-speech" levels. He attributes it to an "imperfect control of the motor by the sensory mechanism, if sensory mechanism is understood to include the mechanisms of integration as well as reception." Exceptionally we can recognize in pure or relatively pure form a disorder of auditory phoneme-schemas—pure word-deafness; of central word-schemas, which I have called central aphasia; or of word-meaning schemas, which in my view includes nominal and amnesic aphasia. Much commoner must be a combination of word-deafness with central aphasia, of central aphasia with nominal

XUM

aphasia, or of all three, and I suspect that severe jargon aphasia in which the patient's thought is so disturbed that he fails to recognize his disability, is the product of a combination of a severe form of central and nominal aphasia. On the expressive side again we meet with a pure form in pure word-dumbness, or apraxic anarthria due to loss of motor word-schemas.

The nature of Broca's aphasia is still uncertain. I think it represents the breakdown of a physiological organization intervening between central word-schemas and motor phoneme-schemas, but combinations of Broca's aphasia with apraxic anarthria or central aphasia, or both, must be common.

Here we return to our starting point. What I have just said shows how impossible it is to infer from cases of aphasia the physiological organizations underlying speech. It also shows the inadequacy of purely psychological classifications of aphasia, and still more of the attempt to correlate disturbances which can be classified psychologically with lesions in particular situations. We have seen that the physiological organizations upon which speech depends are of great complexity, extend over considerable areas of the brain, and are organized in time as well as in space. These serve psychological functions, but the breakdown of a physiological schema does not necessarily, or indeed usually, disturb speech in a way that corresponds to a single type of psychological defect. Moreover, the anatomical organization of the schemas means that only rarely will a single type of schema be disturbed in isolation from others. Hence what the clinician calls aphasia is almost always the product of a mixture of physiological disturbances resulting in a complex medley of psychological disabilities. For the present, therefore, the classification of the aphasias must be largely empirical. The task of the future is to use all the available modern methods of psychological testing, linguistics, phonetics, and communication theory, to correlate psychological with physiological functions. Already we can see the directions in which progress is likely to be made. Stanton (1958) has shown that "delayed auditory feedback" may throw light on the disorder of function in aphasia at the sensorimotor level. Alajouanine and Mozziconacci (1948), Alajouanine (1956) and Bay (1957*a*, *b*, *c* and *d*, 1960) have studied phonetic disintegration, and Bay has also investigated the relation between aphasia and other types of psychological disorder. Schuell's work has already been mentioned. Probability theory has been applied to normal speech (Miller, 1951; Licklider and Miller, 1951; Fletcher, 1953), and Herdan (1958) has applied it to aphasia in a statistical study of the vocabulary of aphasics. By such investigations we may hope to arrive at an analysis of speech disturbances at both the psychological and physiological levels, and of their interrelationships, which will provide a scientific basis for the recognition of the types of disorder of function present in each individual aphasic patient.

I am grateful to the President and Council of the Royal Society of Medicine for permission to publish this lecture in BRAIN, and to Dr. A. M. Uttley for his helpful comments.

REFERENCES

ALAJOUANINE, T. (1956) *Brain*, **79,** 1.

——, and MOZZICONACCI, P. (1948) "L'Aphasie et la désintégration fonctionnelle du langage," Paris.

BASTIAN, H. C. (1898) " A Treatise on Aphasia and Other Speech Defects." London.

BAY, E. (1957*a*) *Dtsch. Z. Nervenheilk.*, **176,** 553.

—— (1957*b*) *Dtsch. Z. Nervenheilk.*, **177,** 1.

—— (1957*c*) *Pyschiat. et. Neurol.*, **134,** 298.

—— (1957*d*) *Nervenarzt*, **28,** 450.

—— (1960) *Nervenarzt*, **31,** 145.

BERGSON, H. (1896) "Matière et Mémoire." Paris.

BLACK, J. W. (1951) *J. Speech Dis.*, **16,** 56.

BRAIN, W. R. (1950) *in* "Perspectives in Neuropsychiatry." Ed. by D. Richter, London, p. 127.

BROCA, P. (1861) *Bull. Soc. Anthrop. Paris*, **2,** 235.

BROWN, R. W. (1956) "A Study of Thinking." By J. S. Bruner, J J Goodnow and G. A. Austin with an appendix on language by R. W. Brown. New York.

BRYAN, W. L., and HARTER N. (1897) *Psychol. Rev.*, **4,** 27.

—— (1899) *Psychol. Rev.*, **6,** 346.

BÜHLER, K. (1930) "The Mental Development of the Child." London.

CHARCOT, J. M. (1887) "Leçons sur les maladies du système nerveux." Paris **3**, 187.

CONRAD, K. (1954) *Brain*, **77,** 491.

EGAN, J. P. (1948) *Laryngoscope*, **58,** 955.

EISENSON, J. (1938) "The Psychology of Speech." London.

FLETCHER, H. (1953) "Speech and Hearing in Communication." New York, p. 280.

FROMENT, J. (1935) *In* "Traité de physiologie normale et pathologique." Edited by G. H. Roget and L. Binet, **10,** 1229.

GOLDSTEIN, K. (1948) "Language and Language Disturbances." New York, p. 50.

HEAD, H. (1926) "Aphasia and Kindred Disorders of Speech." Cambridge.

——, and HOLMES, G. (1920) "Studies in Neurology," London, **2,** 605.

HERDAN, G. (1958) *Confin. psychiat.*, **1,** 143.

HENSCHEN, S. E. (1920 "Klinische und anatomische Beiträge zur Pathologie des Gehirns." Pt. 5: "Ueber Aphasie, Amusie und Akalkulie." Pt. 6: "Ueber sensorische Aphasie." Stockholm.

—— (1922) "Klinische und anatomische Beiträge zur Pathologie des Gehirns." Pt. 7: "Ueber motorische Aphasie und Agraphie." Stockholm.

HUTCHINSON, J., and JACKSON, J. H. (1861) *Med. Times, Lond.*, **1,** 196.

JACKSON, J. H. (1878*a*) *Brain*, **1,** 313. Reprinted in *Brain*, 1915, **38,** 114, and "Selected Writings," 1931, **2,** 1960.

—— (1878*b*) *Brain*, **1,** 306. Reprinted in *Brain*, 1915, **38,** 108 and "Selected Writings," 1931, **2,** 156.

KLEIST, K. (1959) "Sensorische Aphasien und Amusien auf myeloarchitektonischer Grundlage." Stuttgart.

LASHLEY, K. S. (1951) *In* "Cerebral Mechanisms in Behavior." Edited by L. A. Jeffress. New York. p. 112.

LEE, B. S. (1950) *J. acoust. Soc. Amer.*, **22,** 824.

XUM

LEWIS, M. M. (1936) "Infant Speech." London.
LIBERMAN, A. M., DELATTRE, P., and COOPER, F. S. (1952) *Amer. J. Psychol.*, **65,** 497.
LICKLIDER, J. C. R., and MILLER, G. A. (1951) *In* "Handbook of Experimental Psychology." Ed. by S. S. Stevens, New York, p. 1068.
MACKAY, D. M. (1956) *Brit. J. Psychol.*, **47,** 30.
MILLER, G. A. (1951) *In* "Handbook of Experimental Psychology." Edited by S. S. Stevens. New York. p. 789.
PENFIELD, W., and ROBERTS, L. (1959) "Speech and Brain-mechanisms." Princeton, N. J.
SCHUELL, H. (1950) *J. Speech Dis.*, **15,** 291.
SHOLL, D. A. (1953) *J. Anat., Lond.*, **87,** 387.
—— (1959) *J. Anat., Lond.*, **93,** 143.
—— and UTTLEY, A. M. (1953) *Nature, Lond.*, **171,** 387.
STANTON, J. B. (1958) *Scot. med. J.*, **3,** 378.
UTTLEY, A. M. (1956) "Proc. 1st Int. Cong. on Cybernetics, Namur." p. 830. Paris.
—— (1958) Proc. NPL. Symp. No. 10: "Mechanisation of Thought Processes," **1,** 119.

CENTRAL CORE DISEASE—AN INVESTIGATION OF A RARE MUSCLE CELL ABNORMALITY[1]

BY

W. K. ENGEL, [2,3] J. B. FOSTER,[4] B. P. HUGHES, H. E. HUXLEY[5] AND R. MAHLER[6]

(From the Institute of Neurology and the National Hospital, Queen Square)

INTRODUCTION

CENTRAL CORE DISEASE was first described by Shy and Magee (1956) as "a new congenital non-progressive myopathy" and was named in a subsequent paper (Greenfield, Cornman and Shy, 1958). The original report concerned five persons with proximal muscle weakness in three generations of the "S" family, in which the disease appeared as an incompletely dominant genetic trait. The outstanding histological characteristic was the appearance of a central "core" region in almost every muscle fibre. We do not know of any other recorded cases of this disease. (Dr. J. Bethlem has kindly shown us the muscle biopsy sections from a recently discovered case in Holland (1960).)

The present report concerns another patient who was found to have Central Core Disease. He was clinically rather similar to the cases of Shy and Magee, except that extensive inquiry into the family history did not reveal any other affected members. The initial muscle biopsy showed the presence of central core regions in the muscle fibres. In order that special studies of the muscle tissue could be made, a further biopsy was performed upon the patient, and, in addition, biopsies from his clinically

[1]A summary of this investigation was presented as a demonstration at the Centenary of the National Hospital, Queen Square, June 20–25, 1960.

[2]Holder of a Special Traineeship (BT-433) from the National Institute of Neurological Diseases and Blindness, Bethesda, Maryland.

[3]Present address: Clinical Neurology, N.I.N.D.B., National Institutes of Health, Bethesda 14, Maryland.

[4]Present address: Royal Victoria Infirmary, Newcastle upon Tyne.

[5]Dept. of Biophysics, University College London.

[6]Dept. of Experimental Medicine, Guy's Hospital, London.

XUM

normal parents were obtained. The results of the investigations of this rare muscle cell abnormality are presented in this report.

Case Reports

Son:

Clinical history.—M. D. (N.H. 90056), a 19-year-old male store room clerk, came under the care of Dr. R. W. Gilliatt at the National Hospital, Queen Square, in December 1959, for investigation of muscular weakness present since childhood. The past history revealed that there had been no maternal illness during the pregnancy. A description of the intra-uterine movements was not available. The patient was born normally in hospital at full term, following version of an uncomplicated breech. The birth weight was 6 lb. The milestones of mental development were reached at the appropriate ages. He was said to be "double-jointed" but not "floppy" as a baby. At the age of 2 years he was able to walk. However, he persisted in crawling and preferred to do so, especially on his buttocks, until he was 4 years old. From childhood, he has had to climb up his legs in order to stand erect. His muscular bulk has always been small. At the age of 4 years, he was examined in a hospital and his mother was told that his slowness and difficulty in walking were due to "flat feet".

At school, the patient was a poor runner and much slower in games than his fellows. He always has had specific difficulty in climbing stairs, rising from a chair, or lifting objects above shoulder level. Although aware of the weakness of his "hips" and "shoulders," he insists that elsewhere he is strong and can walk 20 miles without fatigue. There has been no deterioration in his condition since puberty; before that time his strength had increased *pari passu* with his developing musculature. There is no history of muscle pain or cramps or episodes of increased muscular weakness. After sitting down following prolonged standing or walking, the patient often experiences "a shivering feeling without actual movement" in his thighs lasting for about five minutes.

Physical examination.—The general physical examination was within normal limits except for a lumbar lordosis and a loss of the transverse metatarsal arches. The patient was of average intelligence. The only abnormalities revealed on examination of the cranial nerves were slight bilateral weakness of the lower part of the face and slight bilateral weakness and smallness of the sternomastoid and upper trapezius muscles. There was moderate weakness and smallness (fig. 3, Plate XVIII) of the muscles about the shoulders and hips. Somewhat less involved were the muscles of the arms, thighs, and trunk. The muscles of the left side were slightly weaker than those of the right. The distal limb muscles of the forearms, legs, hands, and feet were relatively strong. Whilst the proximal muscles could be described as moderately weak (grade 3–4), the strength of the distal muscles was slightly below that expected in a man of his age and build. No fasciculation, myotonia, hypotonia, or involuntary movements were detected. Co-ordination was good. The biceps, triceps, and knee jerks were barely obtainable, but the radial and ankle jerks were normal. Abdominal and plantar reflexes were normal.

A functional assessment revealed that the patient could walk a virtually unlimited distance on the level without fatigue or development of muscular cramps. Because of muscular weakness, he was unable to sit up from the supine position without the use of his hands. To rise from a low chair or to climb up a 12-inch step without using his hands was very difficult.

Laboratory investigations.—The hæmoglobin, white blood cell count, erythrocyte sedimentation rate, blood Wassermann reaction, blood urea, total serum proteins, paper electrophoresis of serum proteins, serum electrolytes (sodium, potassium, chloride, bicarbonate, calcium, and phosphate), and routine urinalysis were all within normal limits. The blood group was O, Rh positive. The examination of a specimen

of urine in the laboratory of Prof. C. E. Dent revealed sugar, protein, acetone, phenylketone, and cysteine to be absent; calcium, keto-acids, glycine, and taurine to be present in normal amounts; and the amino-acid chromatogram to be normal. Chest X-ray revealed no abnormality, and on screening the diaphragm was seen to move normally.

The electromyographic examination by Dr. P. M. Fullerton of the right triceps and quadriceps muscles with a concentric needle electrode revealed that insertion activity was normal and there was no spontaneous fibrillation. On voluntary contraction, many motor units appeared normal but some were abnormally short and of small amplitude. The interference pattern was full on maximum effort. It was concluded that some motor units showed characteristics of a myopathy.

Family history.—Extensive questioning revealed no manifestations of neuromuscular disease or other inherited disease in any of the 93 close relatives covering four generations of the patient's family (fig. 1).

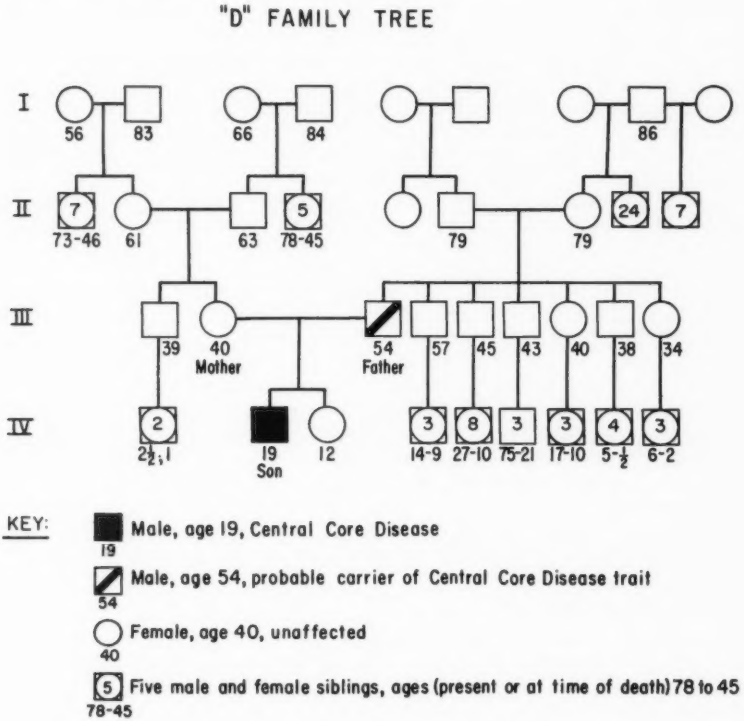


FIG. 1.—Family tree of the present case.

Father and Mother:

The *father* (N.H. 92572) and *mother* (N.H. 92574) were subjected to detailed anamnestic and clinical scrutiny without any significant abnormality being detected. Specifically, with regard to muscular strength, both have been normal throughout their lives. Six weeks prior to muscle biopsy, the *father* had an appendectomy for acute appendi-

citis. The results of the same routine biochemical tests as were done on the *son* were within normal limits for both parents. The urine of the *father* was also examined by Prof. C. E. Dent and was found to be normal with respect to the previously mentioned items. The *father's* blood group was O, Rh positive, as was the *mother's*.

Muscle Pathology

Son (1):

The first biopsy was taken from the biceps brachialis under local anæsthesia and was fixed in Bouin's fluid for twenty-four hours. It was then double embedded in celloidin and paraffin (as were all the biopsies). Numerous stains were used to display the histological features. The details of the staining methods were generally similar to those outlined by Lillie (1954) and Pearse (1960).

Pattern of the lesion.—There was no destruction of isolated fibres and no groups of small fibres.

Muscle fibre size.—Most of the fibres were approximately 60–65 μ in diameter, although a few smaller fibres and some larger fibres up to 130 μ were present.

Muscle fibre structure.—Almost every fibre had a central core region of abnormally staining material which extended the full length of the portion of the fibre obtained in the specimen. The core regions were more often single in the fibre (fig. 5). When more than one core region appeared in a fibre, the fibre diameter was usually greater than 65 μ. There were occasional very large fibres which had no core regions. On cross-section, the core region was roughly circular; on longitudinal section it had parallel borders and did not branch. All the core regions were of fairly uniform diameter, usually, 15–22 μ. The core-to-surface distance in uni-cored fibres was about the same as the core-to-closest-surface distance in multi-cored fibres, usually 15–22 μ. In multi-cored fibres, the inter-core distance was usually 30–40 μ. In the core region, the myofibrils appeared more closely packed together, but they retained their cross-striated appearance (figs. 8–10). There was no membrane around the core region. An area of relative paucity of myofibrils existed between the core and the non-core regions, but it may have been an artifact due to histological processing.

In a few fibres there appeared "vacuoles," which occasionally contained lightly stained material and which were at times loculated. On transverse section, the vacuoles were rounded. They were usually located within or were replacing the central core region. The vacuoles were not accompanied by a reaction of the muscle nuclei or of inflammatory cells.

Muscle nuclei.—There were internal nuclei in occasional medium and large fibres, and they sometimes occurred in rows. Nuclei were not found within the core region or along its borders.

Muscle spindles.—None were found.

Fat, connective tissue, and intramuscular nerves.—There was a slight increase of perimysial and endomysial fatty tissue. The connective tissue and nerves appeared normal.

Staining of the core regions.—The appearance of the core region after staining was recorded as that due to actual staining and not that due to a closer packing of the core region myofibrils. The core region stained more deeply than the non-core region of the same muscle fibre with the following stains (used singly, unless a mixture is indicated in brackets); acid dyes—eosin (hæmatoxylin and eosin), acid fuchsin (Lendrum's milling yellow), picric acid (hæmatoxylin and van Gieson), azocarmine (Heidenhain's azan, fig. 5), and chromotrope 2R; basic dyes—thionin and Ehrlich's hæmatoxylin; Holmes' silver (fig. 8); Heidenhain's iron hæmatoxylin (fig. 9); and Mallory's phosphotungstic acid hæmatoxylin (PAH). With thionin, the core regions did not show

metachromasia. With PAH, the darker staining of the cores was patchy (fig. 10). With the acid dye bromphenol blue, the core regions remained unstained while the non-core regions were darkly stained. The core regions were unstained with the periodic acid Schiff (PAS) stain, both before and after salivary digestion. With the Gomori trichrome (pH 2·4), the core regions were purplish-red and the non-core regions red.

Son (2):

The second biopsy was taken under local anæsthesia from the vastus lateralis. At operation, the muscle appeared softer and more fatty than normal. The biopsy specimen was fixed for twenty-fours in formol saline. Most of the previously mentioned stains were used. Additional stains or different results with the above strains are noted below.

Pattern of the lesion.—Occasionally there was an isolated necrotic muscle fibre undergoing floccular degeneration and phagocytosis (figs. 6 and 7). No "regenerating" muscle fibres were found. There were no groups of small fibres.

Muscle fibre size.—Most of the fibres were approximately 95 μ in diameter, a few were smaller, and some were as large as 175 μ in diameter.

Muscle fibre structure.—The cores were more often multiple than single in the fibre (figs. 14, 15). Fibres with only one core region were usually 65 μ or less in diameter. Otherwise, the structure was the same as noted in the biceps.

Muscle nuclei.—There were frequent internal nuclei in medium and large fibres, and they sometimes occurred in rows. Nuclei were not found within the core region or along its borders.

Motor end-plates.—None were found, using the acetylthiocholine method for cholinesterase.

Muscle spindles.—No definite spindles were found.

Fat, connective tissue, and intramuscular nerves.—There was a moderate increase of perimysial and endomysial fatty tissue. The connective tissue and nerves appeared normal.

Staining of the core regions.—In this biopsy, the core regions were much less obvious with the usual stains than in the first biopsy. They were poorly demonstrated with hæmatoxylin and eosin, hæmatoxylin and van Gieson, and Heidenhain's azan. With PAH, they were poorly demonstrated as lighter staining regions. They were well demonstrated as more darkly staining regions with the basic dyes Anderson's hæmatoxylin and toluidine blue. With toluidine blue, the core regions did not show metachromasia. With bromphenol blue, the cores were well demonstrated as unstained regions (fig. 11). The core regions were PAS-negative before (fig. 12) and after salivary digestion. Part of this biopsy fixed for three hours in Carnoy's 6-3-1 fluid showed the same appearance with the PAS stain. Compared with the non-core regions, the core regions showed no excess of protein with Millon's reagent or naphthylene black and no excess of arginine with the Sakaguchi method (Baker's modification). No amyloid was detected with methyl violet. With methyl green (ether-washed) and pyronin, the core regions in formol saline and Carnoy's fixed tissue stained deeper pink. Prior incubation with ribonuclease (Armour, crystallized, bovine origin, 30 units per mg.) 5 mg. per c.c. at 37° C. for 70 minutes abolished the pink staining of the nucleoli and of the non-core regions, but it did not affect the core regions. Thus it was not demonstrated that the core regions contain excessive ribonucleic acid.

The Gomori trichrome method (pre-staining in hæmatoxylin followed by staining in a mixture of chromotrope 2R and fast green FCF) was used without the hæmatoxylin. Staining solutions were buffered with 0·1 molar acetate at pH's of 1·2, 2·3,

3·9 and 5·1. The usual unbuffered mixture (pH 2·4) was also used. At all pH's tested, the core regions stained differently from the non-core regions, but the exact colour combination varied with the pH. The different colour of the core regions was due to an abnormal staining of the A bands, the I bands, or both, depending on the pH.

Son:

The following features were present in both biopsies of the *son:* (1) the abnormal staining of the core regions was apparent in the A bands, the I bands, or both, depending on the technique used; (2) the core regions usually had the same staining reactions as the severely contracted regions of muscle fibres (fig. 13); (3) the core regions were not more dense in phase contrast illumination; (4) in polarized light, the banded appearance of the core region usually differed from that of the non-core region, but it was not consistently altered in the same manner; (5) the degree of contraction of the core region after histological processing, as judged by the appearance of its cross striations, was often greater than the non-core region of the same muscle fibre.

Father:

The biopsy was obtained under local anæsthesia from the biceps brachialis and was fixed for twenty-four hours in formol saline. Many of the previously mentioned stains were used.

Pattern of the lesion.—There was no definite destruction of isolated muscle fibres. There were no groups of small fibres.

Muscle fibre size.—The usual size was approximately 70 μ in diameter, although some fibres were smaller and some were as large as 95 μ in diameter.

Muscle fibre structure.—Normal. No core regions were found.

Muscle nuclei.—Occasionally, several internal nuclei were found in medium and large fibres, and they sometimes occurred in rows.

Motor end-plates and muscle spindles.—None were found.

Fat, connective tissue, and intramuscular nerves.—Normal.

Mother:

The biopsy was obtained under local anæsthesia from the biceps brachialis and was fixed for twenty-four hours in formol saline. Many of the previously mentioned stains were used.

Pattern of the lesion.—The muscle appeared normal. There was no destruction of isolated fibres and no groups of small fibres.

Muscle fibre size.—The usual size was approximately 55 μ in diameter, although some fibres were smaller and some were as large as 65 μ in diameter.

Muscle fibre structure.—Normal. No core regions were found.

Muscle nuclei.—No internal nuclei were found.

Motor end-plates.—The few present in the specimen appeared to have a normal pattern of cholinesterase distribution.

Muscle spindles.—None were found.

Fat, connective tissue, and intramuscular nerves.—Normal.

Special Studies

I. Enzyme Histochemistry

Histochemical studies of enzymatic activity were done on sections of fresh frozen muscle by Dr. V. Dubowitz. Details of the methods and the results have been briefly recorded elsewhere (Dubowitz and Pearse, 1960).

Son (vastus lateralis):

Oxidative enzymes—Demonstration of each oxidative enzyme was accomplished by incubation of the tissue with the particular substrate and a colourless indicator. As the substrate was oxidized the indicator was reduced to its coloured form, thereby marking the sites of the substrate oxidation. The following eight enzyme systems, generally considered to be located in the mitochondria, all displayed a similar appearance: diphosphopyridine nucleotide (DPN) diaphorase; DPN-linked dehydrogenases (isocitrate, malate, glutamate, alpha-glycerophosphate, and lactate); triphosphopyridine nucleotide (TPN)-linked glucose-6-phosphate dehydrogenase; and succinic dehydrogenase. In the non-core regions, there was the normal appearance of numerous small black dots (fig. 14). However, the non-core regions of all muscle fibres showed equal concentration of enzymatic activity, *i.e.* the normal variation of lightly and heavily stained fibres was absent. In the core regions, the black dots were almost completely absent. The diameter of the core regions with the oxidative enzyme staining was larger (22–30 μ) than with the phosphorylase staining (15–22 μ).

The core region diameter shown with ordinary histochemical staining of fixed tissue resembled that of phosphorylase staining.

Phosphorylase—Glucosan phosphorylase activity was demonstrated by incubation of the tissue with the substrate glucose-1-phosphate, at pH 5·6, in the presence of adenosine-5-phosphate, the newly formed glycogen sub-units "(amyloses") subsequently being fixed with alcohol and stained with iodine. In the core regions, virtually no glycogen sub-units were stained (fig. 15). In the non-core regions, the amount of stained glycogen sub-units appeared normal and about equal in all muscle fibres; the normal variation in their enzymatic activity was absent.

Father and Mother:

Oxidative enzymes and phosphorylase—The normal pattern of lightly and heavily stained muscle fibres was present (figs. 16 and 17). No core regions were found.

II. Electron Microscopy

The preparation of the tissue included osmic acid fixation, phosphotungstic acid staining, araldite (Glauert and Glauert, 1958) or methacrylate embedding, cutting of 200–800 Ångstrom thick sections, and examination with the Siemens Elmiskop I electron microscope and has been described previously (Huxley, 1957). Before fixation, both ends of the muscle tissue had been tied to a stick at resting length.

Son (vastus lateralis):

A. *General*—

1. The transition between the non-core region and the core region was

abrupt. It occurred radially across the distance of 2–4 myofibrils (figs. 18 and 20).

2. The transition zone remained at the level of the same myofibrils for a considerable length of the muscle fibre (fig. 18).
3. Neither a space nor a membrane existed between the non-core region and the core region (figs. 18–21).

B. *In the core region—*

1. Mitochondria were almost completely absent (figs. 18 and 20).
2. The myofibrils were more closely packed together (figs. 18 and 19).
3. The cross striated pattern of the myofibrils was fairly well preserved (figs. 18 and 20).
4. Thick and thin myofilaments and their cross bridges were fairly well preserved (fig. 22).
5. The Z lines were usually widened and zig-zagged; this irregularity was reflected in a zig-zagged alignment of the ends of the thick and thin myofilaments of the adjacent sarcomeres (figs. 18 and 20).
6. A greater irregularity of the Z lines occurred less frequently and was associated with patches of dark material located in neighbouring sarcomeres (figs. 18, 20, and 23).
7. Small patches of complete loss of myofibrillar material occurred infrequently (fig. 23).
8. The myofibrils of the core region, in comparison to those of the non-core region, usually showed approximately 10 per cent shortening of their sarcomeres (fig. 18).

C. *In the non-core region—*

All structures were normal. All of the muscle fibres examined appeared to be similar in that their non-core regions contained large numbers of mitochondria (*cf. father* and *mother*).

Father and Mother:

All structures appeared normal. No core regions were found. The muscle fibres examined appeared to be of two types, some of them containing large numbers of mitochondria throughout the fibre and others containing very few.

III. Muscle Tissue Biochemistry

Phosphorylase—Phosphate released when the substrate glucose-1-phosphate was incubated with the muscle homogenate at pH 6·0 was considered to be indicative of phosphorylase activity in the homogenate (Sutherland and Wosilait, 1956; Schmid and Mahler, 1959). Whether this was a valid assumption will be referred to in the discussion. Phosphorylase activity was measured as micromoles of phosphate released per gramme of tissue in 30 minutes at 30° C. (The method can detect as few

as 2 micromoles of phosphate released.) Activation of the phosphorylase activity was attempted by pre-incubation of the homogenate with 0·02 molar adenosine-5-phosphate (AMP) for eight minutes. In each patient, phosphorylase activity was determined in two separate portions of muscle without activation and in a third portion with AMP activation. All assays were done in duplicate, each figure given below representing the average of two results.

	Unactivated I	*Unactivated II*	*Activated with AMP*
Normal	60–150	60–150	100–200
Son	0	0	10
Father	0	0	58
Mother	113	75	194
1/2 Son plus 1/2 Mother	—	—	150

These figures show that without activation there was no phosphorylase activity (*i.e.* no phosphate was detected to have been released) in the muscle homogenate of the *son* (vastus lateralis) and the *father*, whereas activity in the *mother* was normal. With AMP activation, a small amount of phosphorylase activity was found in the *son*, a moderate amount in the *father*, and a normal amount in the *mother*. Incubating tissue from the *son* with tissue from the *mother* did not produce inhibition of the normal phosphorylase activity of the latter.

Pyruvate and lactate after exercise—Exercise was accomplished by stepping on and off a 12-inch step 25 times per minute for 10 minutes.

Son:

The blood pyruvate and lactate (Dr. B. McArdle) were studied before exercise and at 1, 6, 13 and 20 minutes after exercise. The corresponding figures were: (*a*) pyruvate—0·55, 2·36, 1·80, 1·26 and 0·99 mg. per 100 grammes of blood; and (*b*) lactate—9·0, 52·2, 31·4, 23·0 and 19·5 mg. per 100 grammes of blood. Both pyruvate and lactate showed a normal rise after exercise.

Father:

Blood pyruvate and lactate were studied before exercise and at 2 minutes after exercise. The corresponding figures were: (*a*) pyruvate—1·08 and 2·17 mg. per 100 grammes of blood. (*b*) lactate—13·0 and 77·5 mg. per 100 grammes of blood. Both pyruvate and lactate showed a normal rise after exercise.

Fat—The fat content of a separate portion of muscle was measured as milligrammes per gramme of wet tissue (the percentage of fat is given in brackets).

XUM

Son: 121 (12 per cent); *Father:* 5 (0·5 per cent); *Mother:* 4 (0·4 per cent). The amount of fat in the muscle tissue of the *son* was markedly elevated, but it was normal in the *father* and the *mother*.

Glycogen—The glycogen content of a separate portion of muscle was measured (method of Good *et al.* 1933) as milligrammes per gramme of wet tissue (the percentage of glycogen is given in brackets).

Son: 4·05 (0·4 per cent); *Father:* 4·7 (0·5 per cent); *Mother:* 10·05 (1 per cent).

These values are all within normal limits. In the *son* it was noticed at the end of hydrolysis with 5 N sulphuric acid that there still remained some whitish material in the solution obtained from the muscle. The nature of this material has not been identified.

COMPARATIVE SUMMARY

	Son	*Father*	*Mother*	"*S*" *Family*
Proximal muscle weakness from an early age ..	Yes	No	No	Yes
Clinical evidence of progression	No	—	—	No
Dominant inheritance pattern	Possibly	Unknown	Unknown	Yes
Central core regions in muscle fibres ..	Yes	No	No	Yes
Core regions PAS positive after diastase ..	No*	—	—	Yes‡
Absent mitochondria in the core region	Yes	—	—	Not discussed
Additional histological evidence of an "active myopathy"	Yes*	No	No	No
Absent "phosphorylase activity" in muscle homogenate	Yes	Yes†	No	Not tested
Abnormal electrophoretic pattern of muscle sarcoplasmic proteins ..	Yes	No	Not tested	Not tested

*Difference of the *son* from members of "S" family (Shy and Magee, 1956).

†Evidence of abnormality in the *father*.

‡Recent histochemical studies by F. Seitelberger (in press) of muscle from a member of the "S" family have modified and extended the original findings.

IV. Electrophoresis of Muscle Sarcoplasmic Proteins

Muscle sarcoplasmic proteins were extracted and spread electrophoretically in a starch gel. The methods were generally similar to those described elsewhere (Hughes, 1959), except that electrophoresis was carried out in a 0·03 molar Tris (hydroxymethyl)aminomethane-boric acid

buffer at pH 7·7, instead of the phosphate buffer originally employed. Under the standardized conditions, in a certain region of the protein spread three bands, termed for this discussion "A", "B", and "C", are normally present.

Son: Band "B" was absent (fig. 4A). Bands "A" and "C" appeared normal as did the rest of the protein spread.

Father: The normal pattern was present, including bands "A", "B", and "C" (fig. 4B).

The chemical nature of the material in band "B" is not yet known.

Muscle tissue aldolase—Aldolase activity was determined in relation to the protein nitrogen in the sarcoplasmic extracts. In the *son* it was at the lower limits of normal, while in the *father* it was in the middle of the normal range.

Discussion

Pathology

(1) Central core regions were present in almost every muscle fibre of the two biopsies (biceps brachialis and vastus lateralis) from the *son*. No core regions were found in either the *father* (biceps brachialis) or the *mother* (biceps brachialis).

(2) The staining reactions of the core regions, both absolutely and in comparison with the non-core regions, varied considerably in the two biopsies of the *son*. This variation seemed to be related to the fixative and the state of contraction of the muscle tissue when fixed. Therefore, when searching for core regions in a suspected case of Central Core Disease, non-contracted muscle should be put into more than one fixative and then stained by several methods.

(3) By all the tests used in this study, the non-core regions of the muscle fibres of the *son* appeared normal, except that there was an abnormal uniformity of their enzymatic histochemical reactions and of the number of mitochondria they contained.

(4) The abnormal staining of the myofibrils along the length of the core region, as shown with most of the histological stains, appeared more prominent and more generalized than the anatomical derangement of the myofibrillar structure as shown by electron microscopy. This suggested a chemical alteration of certain morphologically normal myofibrillar structures or of their immediate environment.

(5) The manifestations of the abnormal staining of the core region varied when a given dye was employed at different pH's and when dyes of somewhat similar character (e.g. azocarmine and bromphenol blue, both acid dyes) were tested separately. It was interpreted that in the core region the chemical alteration responsible for the abnormal staining was complex, being determined by chemical groups which were different, depending on the pH and on the dye used.

XUM

(6) With most of the ordinary histological stains, the core regions were stained the same as severely contracted regions. It may be that the chemical alterations of the core region myofibrils were similar to the chemical changes occurring in the severely contracted regions of normal myofibrils.

(7) The absence of mitochondria in the core regions as demonstrated by electron microscopy was probably the basis of the lack of mitochondrial oxidative enzyme activity there.

(8) In the core region, glycogen sub-units were not observed to have been made from glucose-1-phosphate under the histochemical conditions which were employed. This may have indicated a reduced amount of sarcoplasm and/or endoplasmic reticulum in the core regions.

(9) The electron microscopic appearance of the core region was unlike that in experimental ischæmia of mouse muscle (Moore, Ruska, and Copenhaver, 1956), late lactation (vitamin E deficient) paralysis in suckling rats (Rumery and Hampton, 1959), muscular dystrophy of humans and mice (Van Breemen, 1957), and "familial periodic paralysis" (Gruner and Porte, 1959).

(10) In the *son*, in addition to the presence of core regions, there was occasional but definite evidence of active muscle fibre degeneration. Perhaps the abnormal muscle fibres had a marginal ability to survive, resulting in their occasional destruction. Yet, this degeneration was not manifest clinically as progressive muscular weakness. In the muscle fibres of the *father*, the number of internal nuclei was more than is normally seen, but the significance of this was not certain.

Biochemistry

(1) There was a definite biochemical abnormality in the *son* and in the *father* affecting the entire muscle homogenate in regard to the liberation of phosphate from glucose-1-phosphate. The biochemical test employed, under ordinary circumstances, is considered to indicate phosphorylase activity. However, it was not valid to assume that the only possible explanation of the absence of release of detectable phosphate was a lack of phosphorylase activity. For example, the phosphorylase system may have split off the phosphate from glucose-1-phosphate normally, but the phosphate may have been trapped by a phosphate-hungry substance in the muscle homogenate and thus not have been detected as liberated phosphate. Not tested biochemically *in vitro* were the other aspects of the phosphorylase system. Because this important additional information was lacking, an accurate identification of the biochemical abnormality was not possible. However, the term "phosphorylase activity" will be retained, with reservation, until more information is available.

(2) The apparent conflict between the severe reduction of "phosphorylase activity" found by biochemical techniques and the normal histochemical appearance of "phosphorylase" in non-core regions of the *son*

and throughout the *father's* muscle fibres might be resolved if we could learn (*a*) whether exactly the same biochemical reactions were being tested by the two methods, and (*b*) the quantitative values of the histochemical method.

(3) The biochemical abnormality of "phosphorylase activity" in the *son* and the *father* differed from that in the condition described by McArdle (McArdle, 1951). In the latter condition, no activation of phosphorylase activity can be obtained with adenosine-5-phosphate (Schmid and Mahler, 1959). Two other differences of the *son* and the *father* from McArdle's disease were that in them: (*a*) exercise did not produce painful muscular cramps and (*b*) there was a normal rise of blood pyruvate and lactate after exercise.

(4) The band labelled "B", normally present in the electrophoretic spread of the sarcoplasmic proteins, was absent in the *son* but present in the *father*. Its loss probably reflected a substance (or substances) missing only in persons with the full clinical disease.

(5) However, neither the primary biochemical abnormalities causing Central Core Disease nor the biochemical steps in its pathogenesis have yet been identified.

Inheritance

(1) It may be that Central Core Disease is inherited as an incompletely dominant genetic trait.

(2) In the fully affected person (*son*), a genetic deficit was probably responsible for the central core regions of the muscle fibres, for the lack of variation between fibres in enzymatic activity and in the number of mitochondria of the non-core regions, and for biochemical abnormalities of the muscle tissue.

(3) It appeared that a probable carrier (*father*) of the trait may show no clinical or histological but definite biochemical evidence of the disease.

(4) Hence, more than one genetic factor must be responsible for the full manifestation of the disease.

Speculation on Pathogenesis

(1) It is probable that Central Core Disease is congenital and that it affects the normal development of muscle fibres. The abnormality of development may occur before the time muscle fibres normally differentiate into ones of high and low oxidative (or phosphorylase) enzymatic activity and ones with different numbers of mitochondria, thereby preventing such differentiation.

(2) The largest diameter of the core region was displayed by the absence of mitochondrial oxidative enzyme activity. The significance of the absence of mitochondria in the pathogenesis of the core regions is not known.

(3) As the abnormal core region involves only a part of the muscle fibre,

XUM

its formation and location must be related to a focal regional abnormality of the fibre, in addition to any widespread abnormality which may exist. Three possible general mechanisms of core region formation are:

(*a*) It may be that the core regions can form anywhere (at the surface or in the central region) in the muscle fibre and be single or multiple. Yet, when the fibres are fully developed the core regions are usually central and of fairly uniform size and location. This possibility is loosely defined and difficult to analyse.

(*b*) Formation of the core region may be based on an abnormality, located at (or near) the cell surface, which is active only during the early stages of muscle fibre development (fig. 2A). In the early stages, the abnormal core region (or regions) would be formed at the cell surface, but subsequently it would be gradually isolated from the cell surface by surrounding non-core region. This mechanism does not invoke a hypothetical fusion of muscle fibres to produce the multi-cored fibres. In the *son*, only very rarely was a core region found to be touching the cell surface.

(*c*) Formation of the core region may be related to regional biochemical peculiarities of the central region of the normal muscle fibre, especially in regard to its embryonic development. In the developing muscle cell (myoblast and myotube stages), there are definite periphery-to-centre gradients of several known biochemical factors (*e.g.* ribonucleic acid). Doubtlessly, there are gradients of many unknown biochemical factors also. Some cell components (*e.g.* myofibrils) appear to develop first at the periphery of the muscle cell and later in the centre. (It would be of interest to know if this applies to mitochondria.) It may be that the abnormality responsible for the production of central core regions manifested itself at an early stage of muscle cell development and caused in almost every muscle cell the appearance of a single core region centrally with a normal non-core region around the periphery.

(4) In considering the third general mechanism, the presence of normal non-core regions deep within the most central part of large multi-cored fibres requires explanation. In muscle fibres 65 μ or less in diameter, the core regions were usually single, and they were usually multiple in fibres with a diameter greater than 65 μ. In small and large fibres, the core regions had approximately the same diameter. The inter-core distance in multi-cored fibres was about twice the core-to-closest-surface distance of uni-cored or multi-cored fibres. These measurements suggest that the appearance of more than one core in a large muscle fibre may have been the result of that fibre having been formed by the fusion of two or more embryonic muscle fibres, each one thus having contributed a single previously developed central core region (figs. 2B, C, D). Both the location and spacing of multiple core regions in larger fibres and certain studies of the development of skeletal muscle fibres (De Rényi and Hogue, 1934; Firket, 1957; Lash *et al.* 1957) lend support to this suggestion.

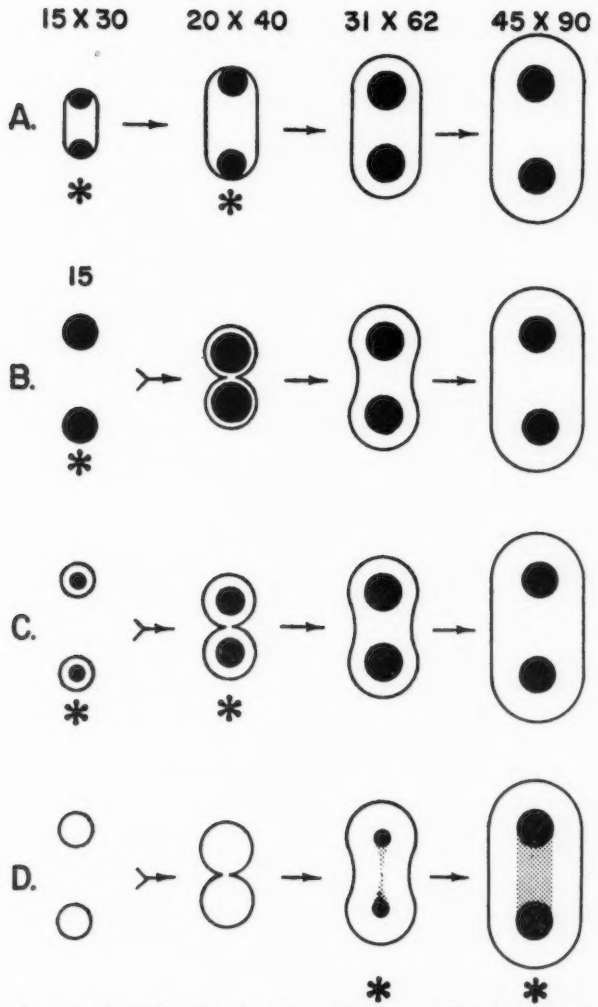


FIG. 2.—Diagram of four hypothetical methods of core region formation in a multi-cored fibre, as related to muscle fibre development. The approximate muscle fibre diameter in micra is indicated for each stage. The starred stages are the ones in which the core region is actively developing.

(5) The third general mechanism may have operated in one of the following ways:

(*a*) There may have been a "block" in the early development of the muscle fibre, initially causing the entire fibre to be core region (fig. 2B).

After a time, the block ceased to act and the newer non-core region was formed at the periphery. The core region would have thus not increased in size, but would have remained as a central abnormal area. However, it is doubtful that all-core embryonic muscle fibres could survive.

(*b*) A "block" in the early development of the muscle fibre may have caused only the centre of the fibre to be core region, with normal non-core region being formed at the periphery (fig. 2C). For a while, the muscle fibre increased in diameter by new non-core region being formed peripherally, but simultaneously the central core region also expanded. After the core region reached its final diameter, the block ceased to act, allowing the fibre diameter to increase by addition of more non-core region.

(*c*) The peripheral (non-core) part of the muscle fibre may have developed earlier and normally. Then a "block" occurred, causing any later developed (central core) region lying more than a certain distance from the surface membrane to be abnormally formed (fig. 2D.) This would mean that as the muscle fibre diameter increased, its core region would have also expanded. However, this would have produced conjoined core regions in the central parts of the large rounded fibres (stippled region, fig. 2D).

(6) Careful measurements of the fibre diameter, core region diameter, and core location in the muscle fibres of an infant or fœtus with this disease might help to decide between the five possibilities outlined above.

Summary

An extensive investigation of Central Core Disease has been presented. The patient, a 19-year-old male, had a non-progressive proximal muscle weakness evident since the first few years of life. Histological examination of the muscle biopsy revealed the presence of one or a few abnormally staining central "core" regions in nearly every muscle fibre. No other persons in a large pedigree were clinically affected. Detailed studies of muscle biopsies from the patient, as well as from his clinically normal parents, included ordinary histology and histochemistry, enzyme histochemistry, electron-microscopy, and tissue biochemistry. The results of these studies and their possible significance have been discussed.

Acknowledgments

We wish to express our appreciation to the following persons: Dr. R. W. Gilliatt for permission to study the patient; Prof. W. Blackwood for advice and for the use of laboratory facilities; Dr. V. Dubowitz for the enzyme histochemical studies and for permission to publish photographs thereof; Dr. B. McArdle for advice and for assistance with some of the biochemical studies; Mr. A. T. Greenway and his technical staff for the histological preparations; and Mr. J. A. Mills for the photographic work.

REFERENCES

BETHLEM, J., and Posthumus MEYJES, F. E. (1960) *Psychiat., Neurol., Neurochir.*, **63**, 246.
DE RÉNYI, G. S., and HOGUE, M. J. (1934) *Arch. exp. Zellforsch.*, **16**, 167.
DUBOWITZ, V. and PEARSE, A. G. E. (1960) *Lancet*, **2**, 23.
FIRKET, H. (1957) Dissertation, les Universites de l'Etat Liège.
GLAUERT, A. M. and GLAUERT, R. H. (1958) *J. biophys. biochem. Cytol.*, **4**, 191.
GOOD, C. A., KRAMER, H., and SOMOGYI, M. (1933) *J. biol. Chem.*, **100**, 485.
GREENFIELD, J. G., CORNMAN, T., and SHY, G. M. (1958) *Brain*, **81**, 461.
GRUNER, J. E. and PORTE, A. (1959) *Rev. neurol.*, **101**, 501.
HUGHES, B. P. (1959) *Biochem. biophys. Res. Comm.*, **1**, 194.
HUXLEY, H. E. (1957) *J. biophysic. biochem. Cytol.*, **3**, 631.
LASH, J. W., HOLTZER, H., and SWIFT, H. (1957) *Anat. Rec.*, **128**, 679.
LILLIE, R. D. (1954) "Histopathologic Technic and Practical Histochemistry." 2nd edition, New York.
MCARDLE, B. (1951) *Clin. Sci.*, **10**, 13.
MOORE, D. H., RUSKA, H., and COPENHAVER, W. M. (1956) *J. biophysic. biochem. Cytol.*, **2**, 755.
PEARSE, A. G. E. (1960) "Histochemistry." 2nd edition, London.
RUMERY, R. E. and HAMPTON, J. C. (1959) *Anat. Rec.*, **133**, 1.
SCHMID, R., and MAHLER, R. (1959) *J. Clin. Invest.*, **38**, 2044.
SEITELBERGER, F., WANKO, T., and GAVIN, M. A. (in press) *Acta Neuropath.*
SHY, G. M., and MAGEE, K. R. (1956) *Brain*, **79**, 610.
SUTHERLAND, E. W., and WOSILAIT, W. D. (1956) *J. biol. Chem.*, **218**, 459.
VAN BREEMEN, V. L. (1957) *Anat. Rec.*, **127**, 486.

LEGENDS FOR PLATES

PLATE XVIII

FIG. 3A, B.—*Son*: The patient, M. D., with Central Core Disease.

FIG. 4A.—*Son* (2): Electrophoretic spread of the sarcoplasmic proteins. Note the absence of band "B".

FIG. 4B.—*Father*: Electrophoretic spread of the sarcoplasmic proteins. All bands appear normal, including band "B".

PLATE XIX

FIG. 5.—*Son* (1): Heidenhain's azan stain. The deeply stained regions within the muscle fibres are the central "core" regions. The fibres with single core regions are approximately 60–65 μ in diameter.

FIG. 6.—*Son* (2): Hæmatoxylin and eosin stain. An isolated muscle fibre is undergoing degeneration and phagocytosis by macrophages.

FIG. 7.—*Son* (2): Hæmatoxylin and eosin stain. An isolated muscle fibre shows degeneration, basophilic cytoplasm, and phagocytosis by macrophages. Internal nuclei appear in an adjacent fibre.

PLATE XX

FIG. 8.—*Son* (1): Holmes' silver stain. In the non-core region there is moderate staining at the edges of the I bands and faint staining throughout the I bands. In the core region the staining in these two locations is darker.

FIG. 9.—*Son* (1): Heidenhain's iron hæmatoxylin stain. In the non-core region the A bands and Z lines are moderately stained and the I bands are unstained. In the core region the A bands are darkly stained, the I bands are moderately stained, and the Z bands are moderately stained.

XUM

FIG. 10.—*Son* (1): Phosphotungstic acid hæmatoxylin stain. In the non-core region the A bands are moderately stained, the Z lines are lightly stained, and the I bands are unstained. In the core region the Z bands are widened and more prominent, in patches the I bands are stained, and the A bands are moderately stained. (Compare this with figs. 18 and 20.)

FIG. 11.—*Son* (2): Bromphenol blue stain. In the non-core region the A bands and Z lines are moderately stained. In the core region they are unstained.

FIG. 12.—*Son* (2): Periodic acid Schiff stain, before salivary digestion. In the non-core region, transverse bands (probably indicating glycogen) are well stained. There is no staining in the core region. The faintly cross-striated appearance of the core region is not due to staining.

FIG. 13.—*Son* (2): Bromphenol blue stain. The core region is stained the same as the severely contracted region at the bottom of the figure.

PLATE XXI

FIG. 14.—*Son* (2): An oxidative enzyme, DPN diaphorase. Black dots, which probably represent mitochondria, indicate the sites of enzymatic activity. They appear normal in the non-core region but are almost completely absent from the core region. The staining of the non-core regions of all the fibres appears equal.

FIG. 15.—*Son* (2): Glucosan phosphorylase. Sites of the enzymatic activity appear dark in a lace-like pattern around the myofibrils. Activity is almost completely absent in the core regions. The staining of the non-core regions of all the fibres appears equal.

FIG. 16.—*Father*: DPN diaphorase. The normal appearance of fibres with high and with low oxidative enzyme activity is present. Core regions are absent.

FIG. 17.—*Father*: Glucosan phosphorylase. The normal appearance of fibres with high and low enzymatic activity is present. Core regions are absent.

PLATE XXII

FIG. 18.—*Son* (2): Electron-micrograph of longitudinal section through part of one muscle fibre, showing abrupt transition from normal to core region along a line parallel to fibre axis. In the core region (delineated by dotted line), the division of the muscle substance into separate myofibrils is much less apparent than in the normal regions of the same fibre. The sarcomere length in the core is less than elsewhere, the decrease in length being represented by a decrease in the length of the I-bands, as one normally finds in shortened muscle. The alignment of the pattern of striations in the core region is disturbed by small local irregularities which produce a very characteristic appearance most easily recognised at the -z- lines. In some regions, the pattern of striations is entirely lost and is replaced by patches of dense material which may extend over several sarcomeres. Mitchondria, which can be seen in substantial numbers in between the fibrils in the non-core region, appear to be completely absent from the core. ×2,250.

FIG. 19.—*Son* (2): Electron-micrograph of transverse section, showing part of one muscle fibre. Central core region delineated by dotted line. Edge of fibre at top of picture. Within the core, the division of the muscle substance into separate myofibrils can again be seen to be much less distinct than in the rest of the muscle fibre, inter-fibrillar spaces are largely absent in the core, as are mitochondria. The imperfection in the alignment of the striations can be recognized by the "pie-bald" appearance of the tissue where the section (which is not quite accurately transverse to the striations, and therefore passes successively through the different bands) has passed through the -z- line region. ×5,000.

XUM

PLATE XVIII

3a

3b

4a

4b

To illustrate article by W. K. Engel, J. B. Foster, B. P. Hughes, H. E. Huxley and R. Mahler.

PLATE XIX

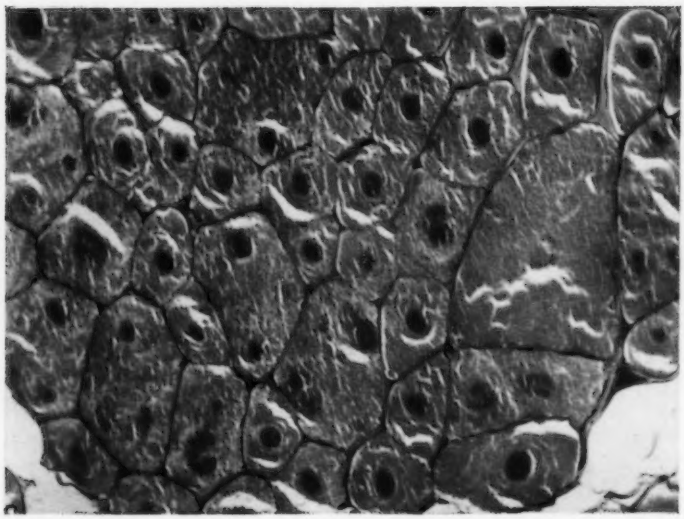
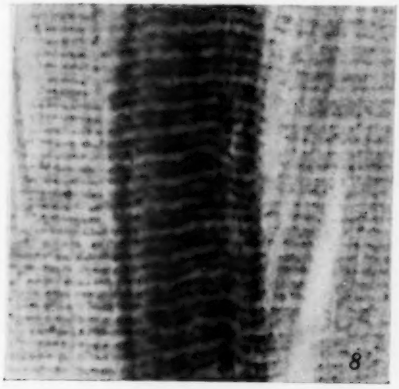
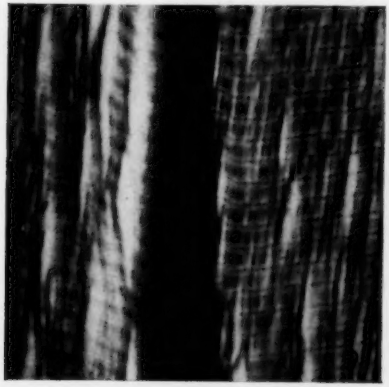


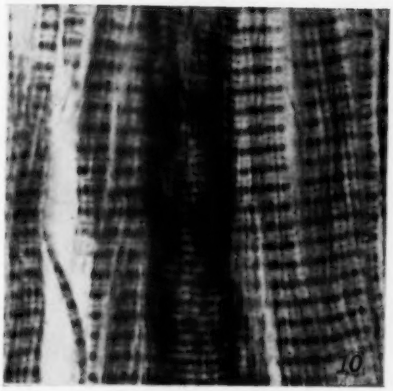
FIG. 5.

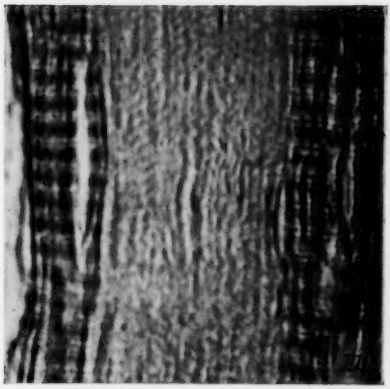
To illustrate article by W. K. Engel, J. B. Foster, B. P. Hughes, H. E. Huxley and R. Mahler.

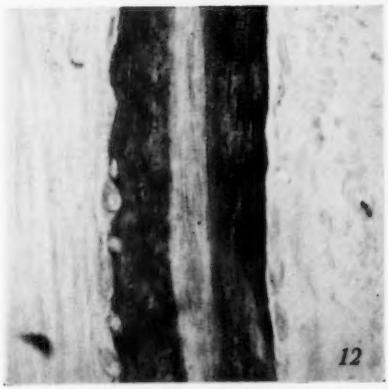
PLATE XX





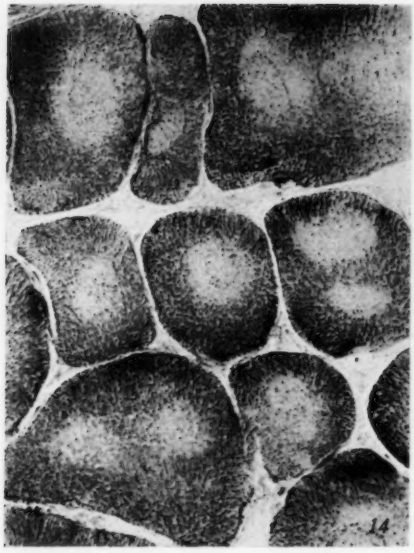


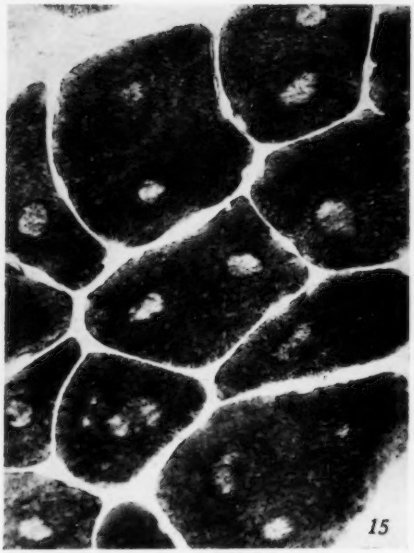


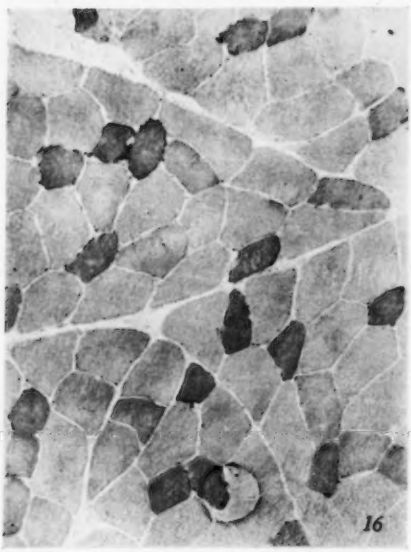


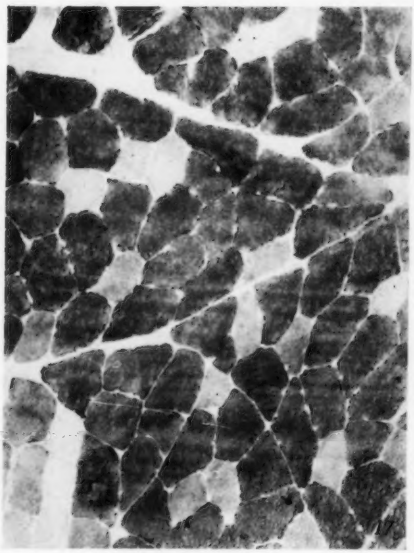
To illustrate article by W. K. Engel, J. B. Foster, B. P. Hughes, H. E. Huxley and R. Mahler.

PLATE XXI









To illustrate article by W. K. Engel, J. B. Foster, B. P. Hughes, H. E. Huxley and R. Mahler.

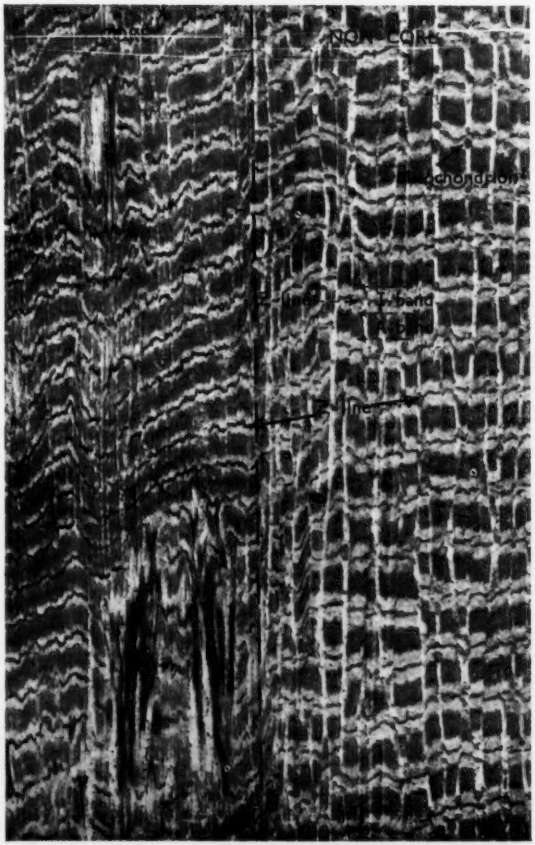


FIG. 18.

FIG. 19.

To illustrate article by W. K. Engel, J. B. Foster, B. P. Hughes, H. E. Huxley and R. Mahler.

FIG. 20.

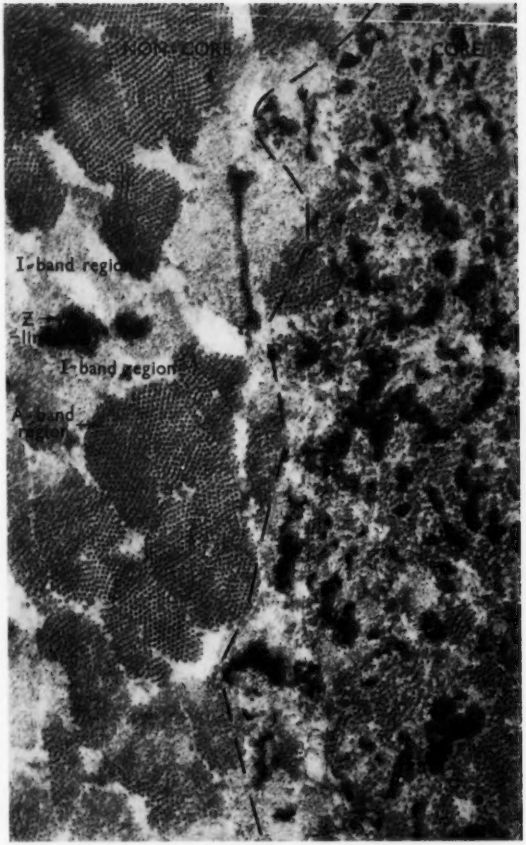
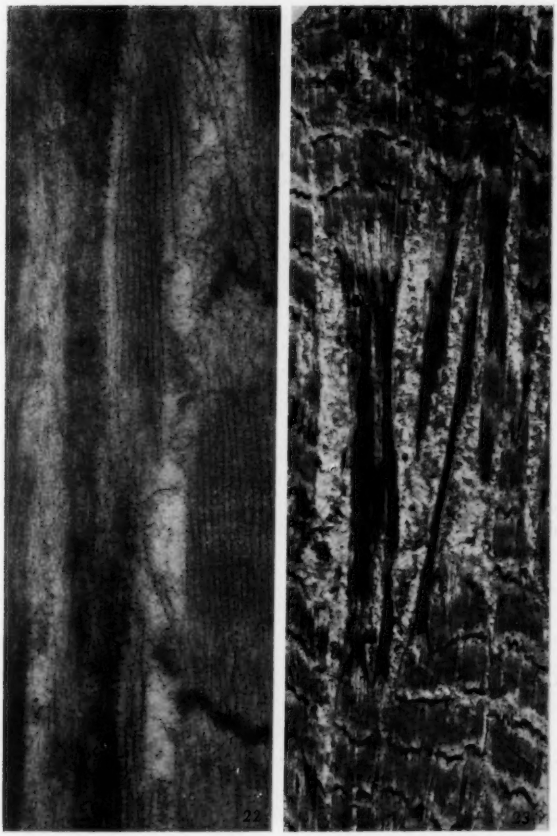


FIG. 21.

To illustrate article by W. K. Engel, J. B. Foster, B. P. Hughes, H. E. Huxley and R. Mahler.

PLATE XXIV



To illustrate article by W. K. Engel, J. B. Foster, B. P. Hughes, H. E. Huxley and R. Mahler.

To illustrate article by W. K. Engel, J. B. Foster, B. P. Hughes, H. E. Huxley and R. Mahler.

XUM

PLATE XXIII

FIG. 20.—*Son* (2): Electron-micrograph showing longitudinal section through core region at higher magnification. In many regions of the core the parallel arrays of myofilaments appear normal; in other regions, they are replaced or overlaid by elongated patches of dense amorphous looking material. Mitochondria, and other structures normally lying between the myofibrils, are either absent or present in much smaller amounts within the core region. The thickening and zig-zagging of the -z- lines may be noted. ×7,500.

FIG. 21.—*Son* (2): Electron-micrograph showing transverse section through adjoining core and non-core regions of a single fibre. The myofilaments may be seen in end-on view, and the double hexagonal array of thick and thin filaments is present in both regions. The effect produced on the appearance of the -z- lines in transverse section by the imperfections in the alignment of the striations can be seen by comparison of those in the core region with those in the normal non-core region. ×25,000.

PLATE XXIV

FIG. 22.—*Son* (2): Electron-micrograph showing very thin longitudinal section through core region, at high magnification. The two types of filaments, with cross-bridges between them, can be seen in several places and appear normal. The elongated patches of dense material in the core have some filamentous character, with an overlay of more amorphous-looking material. ×37,500.

FIG. 23.—*Son* (2): Electron-micrograph of longitudinal section through strongly affected local region of a core, where extensive degeneration appears to be present and where there are regions which contain neither myofibrils nor the patches of dense material but only rather disorganized-looking sarcoplasm. ×3,750.

XUM

THE BENIGN FORM OF MULTIPLE SCLEROSIS. A STUDY BASED ON 241 CASES SEEN WITHIN THREE YEARS OF ONSET AND FOLLOWED UP UNTIL THE TENTH YEAR OR MORE OF THE DISEASE

BY

DOUGLAS McALPINE

(From the Institute of Clinical Research, The Middlesex Hospital Medical School, London, W.1)

THE lack of standard diagnostic criteria in multiple sclerosis continues to prove a handicap when attempts are made to compare the results of group research whether in the clinical and therapeutic fields or in geomedical studies. It is inevitable that any attempt to define these criteria will of necessity express the personal bias of the observer. However, the following five factors would be generally accepted as contributing the essential information on which a diagnosis can be reached: (i) History; (ii) Physical signs; (iii) Behaviour of early symptoms; (iv) Cerebrospinal fluid; (v) Subsequent course of the illness.

When these facets of the clinical picture are considered, a diagnosis can usually be made early in the disease. However, there remains a small proportion of cases in which doubt exists, either because of the unusual clinical picture or paucity of signs. In such circumstances the label "probable" or "possible" may be used until the subsequent occurrence of one or more relapses or the appearance of such signs as an extensor plantar response or pallor of an optic disc clarifies the issue; occasionally qualifying adjectives must be retained because these features of multiple sclerosis do not occur during a lengthy follow-up. It is clear, therefore, that finality on the subject of diagnosis, particularly in the early case, is unlikely to be reached without the aid of a specific test.

PRESENT STUDY

Between 1949 and 1950, the notes of all cases diagnosed as multiple sclerosis at the Middlesex Hospital from 1930 onwards were used for a study of the natural history of the disease (McAlpine and Compston, 1952). The total number was 651. The majority of these patients were examined at that time and a follow-up clinic was instituted at which all but the more severely disabled patients were seen at least once a year. After 1955, facilities were provided for the present writer to continue this clinic at the Institute of Clinical Research. An opportunity was thus afforded

of making a prospective study of the course of the disease in a group of patients who had attended the Department for Nervous Diseases and had before the war been examined by the same physician. Between 1941 and 1945, Dr. Paul Sandifer was in charge of this department and with the appointment of Dr. Michael Kremer to the staff in 1946, a proportion of the cases subsequently came under his care.

The patients covered by the present survey were those in whom the disease had begun between January 1930 and December 1949. In Great Britain, death from multiple sclerosis within the first three years of the disease is unusual; however, in order to improve the statistical value of the survey, only those patients who had been seen within this period were included.

As the following figures show, the great majority of patients with suspected multiple sclerosis included in this survey have been admitted for investigation and treatment. Those who only attended the Out-Patient Department on a single occasion have not been included unless the grounds for the diagnosis were reasonably sound.

28 patients were seen as Out-Patients only; 213 were admitted to hospital.

Duplicate copies of the original in-patient and out-patient notes had been made for the purpose of our previous study. These have proved invaluable in reviewing at leisure the diagnosis, more particularly in the more difficult cases. In addition, personal follow-up notes of patients seen each year up till 1959 were available. An analysis sheet was prepared for each patient on which was entered certain basic information, including the nature of the presenting symptoms, the signs noted at the first examination, the findings in the cerebrospinal fluid, the date of each relapse, the degree of disability at each examination, the course of the disease and the form of treatment. Unless a patient was severely disabled or lived far from London, every effort was made to examine him or her each year. The progress of the disease in those, who by reason of increasing disability, became unable to visit hospital was ascertained each year by means of a letter to the general practitioner or to the hospital authority requesting that the degree of disability should be marked according to a formula, of which details are given later. Information regarding the dead was obtained either from the general practitioner or from the Registrar-General's office. Excluded from the survey were 17 patients who could not finally be traced; of these 14 were seen between 1930 and 1939.

Diagnostic Classification

One of the advantages of a prospective study is the opportunity it affords of reviewing from time to time and, if necessary, modifying the original diagnosis. The passage of years may provide additional *positive* evidence to support the diagnosis of multiple sclerosis, either by the appearance of a symptom highly characteristic of the disease, e.g. a retrobulbar neuritis, or by the occurrence of relapses. On the other hand, in non-relapsing cases the continued failure to arrive at an alternative explanation of the patient's original illness may be used, with discretion, as *negative* evidence in support of the original diagnosis.

The following diagnostic categories have been employed in analysing the results of the present survey. As already stated the original diagnosis, except for one case with the alternative diagnosis of acute disseminated encephalomyelitis, was multiple (or disseminated) sclerosis, qualified in a number of instances by an interrogation mark or by the adjectives "probable," "possible" or "suspect."

XUM

Definite.—(1) A history of an acute retrobulbar neuritis or of an episode of paræsthesiæ, motor weakness, double vision, unsteadiness in walking or other symptom known to occur in multiple sclerosis which tended to improve or clear up, followed by one or more relapses during the course of years with, in addition, the presence of pyramidal and other signs indicative of multiple lesions in the central nervous system when the patient was first seen or subsequently. In mild cases these signs may remain minimal for many years.

(2) A gradual onset of a paraplegia later followed by relapses and signs indicative of disease in brainstem, cerebrum or optic nerve.

Probable.—(1) During the original attack clinical evidence of multiple lesions which, at the time, suggested the probability or possibility of multiple sclerosis, followed by a good recovery. During a lengthy follow-up, relative or complete absence of fresh symptoms after the first year but with a tendency to variability in pyramidal and other signs originally present or the occasional late appearance of an extensor plantar response, nystagmus, tremor or temporal pallor of a disc.

(2) A history of one or more attacks of acute retrobulbar neuritis accompanied or followed by pyramidal signs, usually mild in degree. Subsequently no clinical evidence of relapse.

Possible.—(1) A history similar to that described under Probable (1) but with unusual features or a paucity of signs, or lack of definite follow-up information.

(2) A history of a progressive paraplegia usually in early middle age without evidence of relapse or remission or of a lesion outside the spinal cord, appropriate investigations, including myelography, having excluded other causes of progressive paraplegia such as cervical spondylosis, spinal cord tumour and motor neurone disease.

Note.—When doubt existed as to the diagnosis, attention was paid to the following (1) the age of the patient; (2) a history of the disease in another member of the family; (3) the findings in the cerebrospinal fluid.

A Classification According to the Degree of Motor Disability

In multiple sclerosis, the major cause of disability arises from motor weakness in one or both lower limbs or to lack of balance or to a combination of these defects. A *qualitative* estimate can be made based primarily on the distance an individual can walk without being forced to rest owing to undue fatigue. When disability exists, the necessity of support when walking, e.g. from one or two sticks, or if the patient is house bound the ability or otherwise to move from room to room by means of support from furniture, must be taken into account.

In the present study I have followed the classification previously used by us (McAlpine and Compston). It does not make allowance for disability due to defective vision, impaired use of the upper limbs or

loss of sphincter control, the last being nearly always associated with some impairment of walking range. In any classification concerning disability, a small proportion of cases will approach the boundary between two categories; however, in a follow-up carried on over a number of years the margin of error becomes small. In those patients in this series who ultimately became too disabled to attend hospital for examination and in whom the category was determined at yearly intervals by general practitioners, the results were on the whole consistent.

(1) *Unrestricted:* Without restriction of activity for normal employment and domestic purposes, but not necessarily symptom-free.

(2) *Restricted:* Able to walk unaided for short distances (up to half a mile) and able to get on and off public transport.

(3) *Markedly restricted:* Capable of moving out of doors with difficulty for up to a quarter of a mile, usually with the aid of sticks; often unable to use public transport.

(4) *Mobile at home:* Able to move with difficulty about the house with support from furniture; unable to mount stairs.

(5) *Immobile at home:* Confined to a chair or wheelchair, and entirely dependent upon others for moving from room to room.

(6) *Bedridden.*

The Results

In analysing the results of the follow-up in this series a broad classification was used as follows: (1) Dead; (2) Disabled; (3) Unrestricted. In the second group the degree of disability ranged from "Restricted" to those patients who were confined to bed.

Table I.—Classification of 241 Cases of Multiple Sclerosis at End of Follow-up Period, i.e. December 1959

	Dead	*Disabled*	*Unrestricted*
No. of patients ..	83 (34%)	80 (33%)	78 (32%)

These figures will be discussed under the appropriate headings and *see* figs. 1 and 2.

Table II.—The Year of the Disease in which Patients were First Seen

	1st year	*2nd year*	*3rd year*
Dead	28 (26%)	37 (48%)	18 (31%)
Disabled.. ..	25 (24%)	23 (30%)	32 (55%)
Unrestricted ..	53 (50%)	17 (22%)	8 (14%)
Total	106 (44%)	77 (32%)	58 (24%)

When the figures are expressed as a percentage of the totals seen in the first, second and third years of the disease, it is apparent that the number of patients seen during the first year of the disease, in whom the

subsequent course of the disease was mild, is significantly higher than in the other two groups.

TABLE III.—AGE OF ONSET AND SEX DISTRIBUTION IN 241 CASES OF MULTIPLE SCLEROSIS

Age	15–19	20–29	30–39	40–49	50>	*Total*	*% of total*
Dead ..	M 4	M 10	M 16	M 11	M 1	42	(46%)
	F 3	F 15	F 13	F 10	F —	41	(28%)
Disabled ..	M —	M 8	M 16	M 2	M 1	27	(29%)
	F 5	F 17	F 21	F 8	F 2	53	(36%)
Unrestricted	M 3	M 9	M 8	M 3	M —	23	(25%)
	F 9	F 15	F 25	F 5	F 1	55	(37%)
	M 7	M 27	M 40	M 16	M 2	92	—
	F 17	F 47	F 59	F 23	F 3	149	—
Total	24 (10%)	74 (31%)	99 (41%)	39 (16%)	5 (2%)	241	

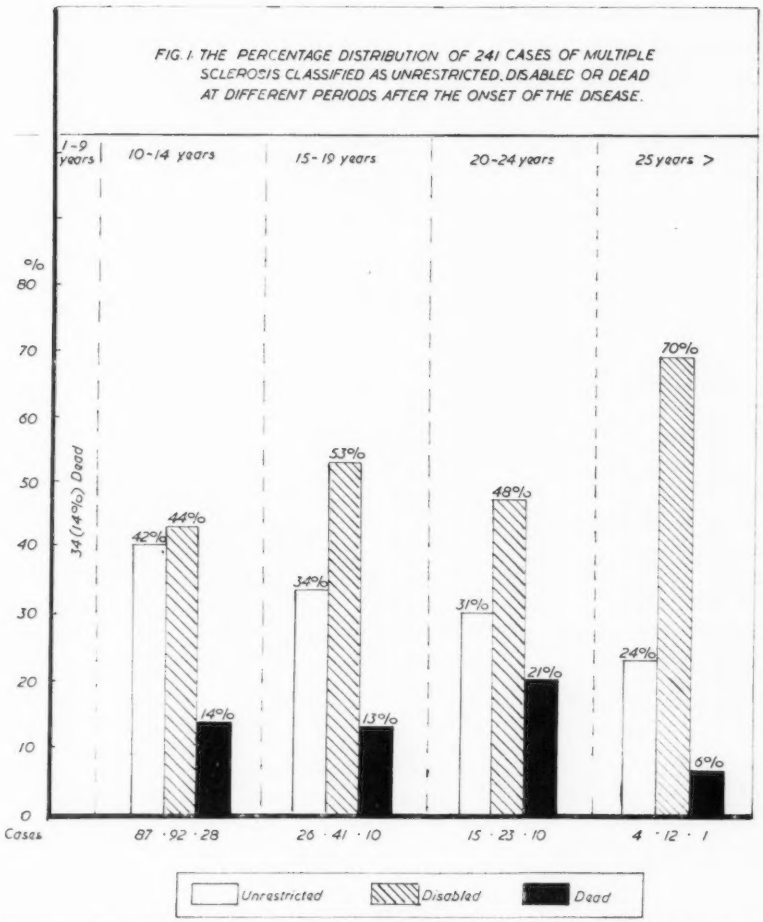
Although when classified, the numbers in each decade are small, there appears to be no significant difference in the age of onset in relation to the subsequent course of the disease. The highest incidence of onset was in the fourth decade, an unusual finding but one which was also present in Allison's and Miller's series of 411 cases in Northern Ireland (1954). When the fatal cases are expressed as a percentage of the total at risk (i.e. 92 males and 149 females) then it appears that 46 per cent of the males have so far died as compared with 28 per cent of the females.

After the fourteenth year there is a sharp fall in the total number of patients and consequently in the statistical value of the figures in each group. Excluding the 62 patients who died within fifteen years, there remain 179 who have survived for this period. 9 of the 87 patients placed in the unrestricted category at this stage subsequently became disabled and remained so. The percentage of patients in the "unrestricted" group declines from 42 per cent at 10–14 years, to 34 per cent at 15–19 years and 31 at 20–24 years while the corresponding figures for the "disabled" are 44 per cent, 53 per cent and 48 per cent.

TABLE IV.—THE COURSE OF MULTIPLE SCLEROSIS IN 241 CASES

	Remittent	*Remittent and Progressive*	*Progressive*
Dead	5	66	12
Disabled.. ..	13	54	13
Unrestricted ..	78	—	—
Total	96 (40%)	120 (50%)	25 (10%)

In 60 per cent of the cases in this series, there was evidence of progression: in the majority, this had followed a single severe relapse or a number of relapses; in a small number it had been in evidence from the



onset. 13 patients in the Disabled group (Category Restricted) showed no evidence of progression in 1959; in 5 of these the disease had lasted more than twenty years and in another 2, sixteen and seventeen years respectively.

TABLE V.— TYPE OF ONSET IN RELATION TO COURSE OF DISEASE IN 241 CASES OF MULTIPLE SCLEROSIS

	Monosymptomatic	*Polysymptomatic*	*Total*
Dead	26 (31%)	57 (68%)	83
Disabled.. ..	41 (51%)	39 (48%)	80
Unrestricted ..	42 (54%)	36 (46%)	78
	109 (45%)	132 (55%)	241

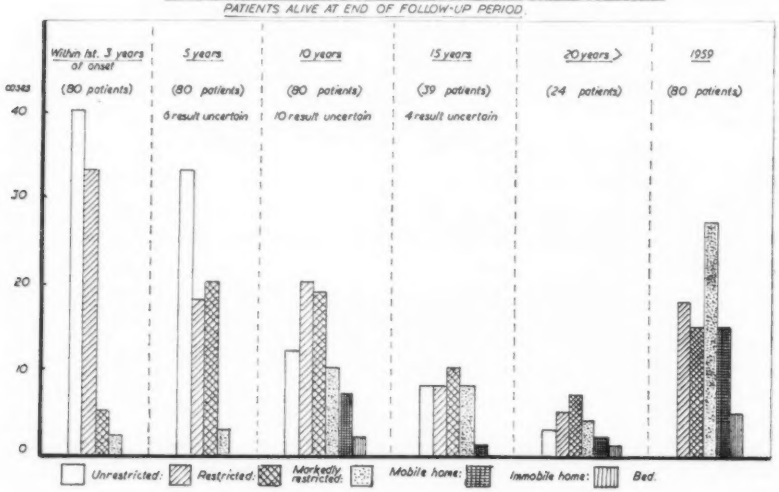
A "monosymptomatic" type of onset implies that one kind of symptom occurred alone, but it does not necessarily follow that there was only one lesion causing the particular symptom. In those patients already dead, a polysymptomatic type of onset was twice as common as a monosymptomatic one. On the other hand, the latter type was seen with equal frequency in those patients who subsequently became disabled as in those who remained well or comparatively so, but by contrast with the fatal cases, the majority of these had had a monosymptomatic onset.

TABLE VI.—DURATION OF DISEASE IN 83 FATAL CASES OF MULTIPLE SCLEROSIS

Years . .	. .	1	2	3	4	5–9	10–14	15–19	20–24	25	*Total*
No. of patients		2	2	1	4	25	28	10	10	1	83

In 9 patients the disease ran a *malignant* course, death occurring within five years. 34 patients died before the tenth year and two-thirds of all who died did so before fifteen years. The average duration of the disease in those who have died was just over eleven years. Reference to Table IV shows that in the majority the disease at first ran a remittent course before becoming progressive. In 12 patients, the disorder was insidiously progressive from the onset. In a number of patients, no information was available as to the course of the disease. In 5 patients, the diagnosis of multiple (disseminated) sclerosis was not entered on the death certificate, the following being given as the cause of death: carcinoma of the lung, carcinoma of the ovary, suicide, coronary thrombosis and cerebral thrombosis. The first three of these patients were seen within a year of death; at that time each was classified as "unrestricted."

FIG. 2. CATEGORIES AT 5 YEAR INTERVALS OF 80 DISABLED MULTIPLE SCLEROSIS PATIENTS ALIVE AT END OF FOLLOW-UP PERIOD.



The Disabled

In this group approximately half of the patients were classified as "unrestricted" when seen within three years of the onset. By the tenth year this figure had fallen to nearly one-seventh. At fifteen years, 8 were still in category "unrestricted" and 18 others were "disabled" but not too seriously, while 9 patients were housebound. At twenty years or more, 4 of the 24 patients were either mildly or markedly "restricted." Of 3 patients still classified as "unrestricted" at the twentieth year, 2 became "restricted" in the twenty-first and twenty-ninth years respectively, while the category of the third patient was reduced to "mobile at home" in the twenty-third year of the disease.

The Unrestricted

78 patients were at the end of the follow-up period considered to be "without restriction of activity for normal employment and domestic life but not necessarily symptom-free." In practice, all these patients were able to walk more than half a mile without a rest or support from a stick and were either working away from or at home.

Table VII shows the duration of the disease when the follow-up was terminated at the end of 1959: it underlines the limited period of observation of these patients, since, in only a quarter of them have fifteen years elapsed since the onset of the disease. With one exception, all of the 46 "definite" cases were personally examined at the end of the follow-up period. Amongst the 20 "probable" cases there were three who failed to attend in 1959. Here practitioners' reports had to be relied upon as well as in 7 out of 12 cases classified as "possible."

TABLE VII.—CLASSIFICATION AND DURATION OF DISEASE IN 78 CASES OF MULTIPLE SCLEROSIS IN CATEGORY UNRESTRICTED IN DECEMBER 1959

	Years of disease							
	10	11	12	13	14	15–19	20–24	25
Definite	46	34	24	20	18	11	7	2
Probable	20	14	10	6	3	2	1	—
Possible	12	11	9	7	7	6	4	2
Total No. of patients	78 (100%)	59 (75%)	43 (55%)	33 (42%)	28 (36%)	19 (24%)	12 (15%)	4 (5%)

Because of the relatively high percentage (32) who came into this category, it became necessary to examine critically the grounds on which the original diagnosis had been made and the degree of probability underlying it, as judged by subsequent events. As a first step the copies of the original notes and those made subsequently were re-examined, particular attention being paid to those cases in which a qualifying adjective such as "probable," "possible" or "suspect" had been added

to the diagnosis of multiple sclerosis. In a few instances, it was found necessary to interchange them and three patients previously considered as "definite" were moved into the "probable" category.

In 16 of the 20 "probable" cases, the first part of the definition as given under this heading applied. When first examined, each showed clinical evidence of multiple lesions in spinal cord (3 cases), brain-stem (4 cases), or in both of these situations (9 cases). In the majority, the onset was acute, the clinical picture developing rapidly over the course of a few days. In 14 of these patients, there was no clear indication of a relapse after the first year of the disease; however, some variation in pyramidal and other signs was usual, while in a minority fresh signs appeared during the course of the follow-up period.

As already stated, 12 cases have been labelled as "possible" because of some atypical feature, or, more usually, on account of an inadequate follow-up. They all belong to Type 1 of the definition under this heading. The average duration of the disease in these patients was eighteen years, the shortest period being ten years and the longest twenty-seven years.

In considering the category of these patients at the onset and during the course of the disease, the 12 "possible" cases have been omitted, since in some adequate follow-up information was not available. Of the remaining 66 cases, 54 were in category "unrestricted" when first seen and remained in this category at five and ten years or longer. This does not imply that in some patients the category was not temporarily lowered to "restricted" following a relapse during the intervening years, nor was the possibility overlooked that a lower category might have been imposed for a time had more patients been seen during the initial attack. At the onset 5 patients were "restricted," 2 "markedly restricted" and 1 "mobile at home." However, at five years all were in category "unrestricted" with the exception of 1 patient who remained "restricted" for more than fifteen years before being placed in category "unrestricted." The remaining 7 patients were temporarily placed in a lower category either at five or ten years.

TABLE VIII.—ANNUAL RELAPSE RATE IN 55 CASES OF MULTIPLE SCLEROSIS IN CATEGORY UNRESTRICTED AFTER TEN YEARS OR MORE

	Years of disease																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
No. of relapses	38	35	13	15	11	14	10	16	9	11	3	3	4	1	5	2	1	1	0	1	1
No. of patients	55	55	55	55	55	55	55	55	55	55	35	26	21	15	12	10	10	8	8	7	6
Average No. of relapses each year	·7	·6	·2	·3	·2	·3	·2	·3	·2	·2	·08	·1	·2	·06	·4	·2	·1	·1	0	·1	·1

Of the total number of 78 patients in the "unrestricted" group, 23 had

no significant relapse after the first year; 14 of these have been classified as "probable" and 9 as "possible" cases. In the above table these 23 cases have been omitted.

As expected, the annual relapse rate was at its height during the first two years. In the next eight years, it fell by nearly two-thirds and after the tenth year, there was a further decline. One patient accounted for 7 of the 51 relapses between the fifth and ninth years, for 3 of the 5 relapses in the fifteenth year and for all of those in the fourteenth, sixteenth and seventeenth years.

TABLE IX.—RETROBULBAR NEURITIS AS AN INITIAL SYMPTOM OCCURRING EITHER ALONE OR WITH ONE OR MORE SYMPTOMS IN 241 CASES OF MULTIPLE SCLEROSIS

	Dead 83 *patients*	*Disabled* 80 *patients*	*Unrestricted* 78 *patients*
Retrobulbar neuritis alone	7	9	21
Retrobulbar neuritis with other symptom	9	3	8
Total	16 (20%)	12 (15%)	29 (37%)

This table emphasizes the greater frequency of acute retrobulbar neuritis in the opening phase of the disease in the "unrestricted" group, as compared with the other two groups, in which the course was, on the whole, unfavourable. In the first group, 15 of the 21 cases showed other evidence of the disease within a few years. 3 of the remaining cases were labelled as "probable" and three as "possible," relapses being mild or absent and pyramidal signs relatively inconspicuous.

TABLE X.—INCIDENCE OF MOTOR WEAKNESS IN A LOWER LIMB AND OF UNSTEADINESS IN WALKING AS INITIAL SYMPTOMS IN RELATION TO SUBSEQUENT COURSE OF THE DISEASE IN 241 CASES OF MULTIPLE SCLEROSIS

	No. of patients	*Weakness of one or both lower limbs*	*Unsteadiness in walking (cerebellar)*
Dead	83	50 (60%)	10 (12%)
Disabled.. ..	80	47 (58%)	12 (14%)
Unrestricted ..	78	27 (34%)	11 (14%)

Permanent and increasing disability in multiple sclerosis is due either to a paraplegia or to cerebellar ataxia or to these in combination. In the above table, unsteadiness in walking was assumed to be of cerebellar origin, if neither giddiness nor marked sensory disturbance in the lower limbs were present at the onset; cases with either of these two symptoms have been omitted. As expected, there is a significant difference

XUM

TABLE XI.—PYRAMIDAL SIGNS IN 78 CASES OF MULTIPLE SCLEROSIS CLASSIFIED AS UNRESTRICTED AT END OF FOLLOW-UP PERIOD

Pyramidal signs (*see below*)	*First seen (within three years of onset)*					*Later*						1959					
	0	1	2	3	4	0	1	2	3	4	Unknown	0	1	2	3	4	Unknown
Definite ..	17	10	8	11	1	2	11	8	25	0	1	1	16	10	18	0	1
Probable ..	7	5	3	4	0	1	7	5	3	0	4	3	8	3	4	0	4
Possible ..	3	6	2	1	0	4	2	1	0	0	4	1	2	1	0	0	7
Total	27	21	13	16	1	7	20	14	28	0	9	5	26	14	22	0	12

Key to pyramidal signs:

0 = Reflexes normal apart from unilateral exaggeration in some cases.
1 = Deep reflexes exaggerated, in some cases unequally, with unilateral or bilateral equivocal plantar response.
2 = Unilateral extensor response.
3 = Early bilateral extensor plantar response with mild paresis or normal power.
4 = Well-marked extensor responses with moderate or severe degree of paraplegia.

in the incidence of lower limb weakness in the Dead and Disabled groups as compared with the Unrestricted group. On the other hand, cerebellar ataxia shows roughly the same frequency in all three groups.

In 27 patients (34 per cent) in the "unrestricted" group, signs of pyramidal tract damage were not found at the first examination, while in 21 patients (27 per cent), signs were minimal, consisting of an exaggeration of deep reflexes, often unequally, and a unilateral or bilateral equivocal plantar response. In a number of these patients the abdominal reflexes were abnormal. In the 30 patients (38 per cent) who showed an extensor plantar response (unilaterally or bilaterally), with one exception, the degree of paresis was slight or negligible and spasticity if present, mild in degree. Sustained ankle clonus was only found in a single case for a short time. After some years it will be observed that the percentage of patients whose reflexes remained normal fell off sharply, and the number with bilateral extensor plantar responses nearly doubled. In this last group, this finding sometimes followed a relapse and was temporary, the responses returning to their former state; this accounts for the finding of 6 fewer patients with bilateral extensor responses at the end of the follow-up period than at an earlier date. Several patients, without any subjective awareness of recent limb weakness, were found to have extensor responses for the first time at a routine examination some years after the onset and confirmed on subsequent occasions.

TABLE XII.—THE INCIDENCE OF PYRAMIDAL AND CEREBELLAR SIGNS WITHIN THREE YEARS OF ONSET IN 163 PATIENTS WITH MULTIPLE SCLEROSIS WHO LATER DIED OR WERE DISABLED

		Pyramidal					*Cerebellar*
See key above ..		0	1	2	3	4	
Dead	83 patients	9	8	13	9	44	43
Disabled	80 patients	13	9	11	31	16	35

If the patients in the Dead and Disabled groups be considered together, the incidence of unilateral and bilateral plantar responses in 163 patients when first seen is 70 per cent, compared with 38 per cent in the Unrestricted group. This table also shows that of those patients who subsequently died, 54 per cent were moderately or severely paraplegic within three years of the onset.

Cerebellar signs, consisting of an ataxic gait in the majority, tremor in the minority, were found in 41 per cent of the Dead and Disabled groups at the initial examination. By contrast, in the Unrestricted group only 11 patients (14 per cent) showed some degree of cerebellar disturbance when first seen; a further 9 did so at a later stage. With two exceptions, signs were mild and usually transitory, as shown by the fact that in 1959, in only 9 patients was there evidence of a mild degree of tremor or ataxia,

in an upper limb in 7 and in the form of slight uncertainty in walking in the remaining 2. Such information as was available about those patients, who originally showed cerebellar signs and subsequently died or became severely disabled, suggested that these signs persisted and progressed in severity.

Treatment

The great majority of the patients in this series were admitted to hospital within the first three years of the disease, thus ensuring a period of rest, usually of a month's duration. 45 patients were treated by intravenous novarsenobillon (N.A.B.), 4 courses a year, usually preceded by artificial fever, induced by T.A.B. vaccine, and followed by liquor arsenicalis between courses.

Table XIII.—Treatment by Artificial Fever and N.A.B. in Relation to Subsequent Course of Multiple Sclerosis

Category	*No. of patients*	*T.A.B.*	*N.A.B.*			*Total No. patients treated N.A.B.*
			2 years	*3 years*	*5 years or more*	
Dead ..	83	6	1	3	1	5
Disabled ..	80	14	7	7	5	19
Unrestricted	78	17	4	5	13	22

13 of the 17 patients in the Unrestricted group, treated by artificial fever, subsequently had treatment with N.A.B. for an average period of six years. Of the 14 patients in the Disabled group, similarly treated, 4 were in category Restricted at the end of the follow-up period. One patient had been in category Unrestricted for the first ten years and another for twelve years; 7 other patients originally in this category were finally classified as Markedly Restricted or lower. Tending to nullify any positive conclusion that might be drawn from these results is the fact that roughly three-quarters of the patients finally classified as Unrestricted did not receive this form of treatment. Nevertheless, having witnessed in several patients a downhill course after cessation of several years' treatment with N.A.B. during which they had remained well, it is difficult to avoid the conclusion reached by Cloake in 1946 that prolonged administration of arsenic by injection and orally, preceded by artificial fever, may in some cases of multiple sclerosis favourably influence the course of the disease.

Discussion

In determining the course of a chronic disease such as multiple sclerosis by means of a follow-up of patients, both the sample and the length of follow-up must be adequate. As already stated, the number of patients in the present series was considerably limited by including only those who had been seen within three years of the onset. Since the average

duration of the disease has been calculated to exceed twenty years (Müller, 1949; Allison, 1950; McAlpine and Compston, 1952), theoretically, this should be the minimum length of follow-up, if accurate information about the course of the disease is to be obtained. For obvious reasons, the practical difficulties confronting any single observer in attempting a follow-up of this length are considerable. The minimum period of ten years used in the present series will, therefore, only allow tentative conclusions to be drawn from the results; at the same time some compensation is provided by the fact that they are based upon personal observation. Their main interest lies in the high percentage of patients who at the end of the follow-up period were not disabled and were leading normal lives. Early in its history, the possibility was recognized that multiple sclerosis might run a mild course. In 1872 Charcot wrote . . . "enfin il n'est pas rare de voir des intermissions complètes qui ont pu faire espérer une guérison definitive." Pierre Marie (1895) in discussing the course of the disease, refers to a type with permanent improvement or even recovery and the possibility of arrest during any part of the course. In a follow-up of 200 cases, Byrom Bramwell (1917) found that 7 patients had greatly improved and three were quite well. In 2 of these, thirty-seven and thirty-four years had elapsed since the initial symptoms. As a result of these findings he wrote, "It is probable that in a few rare and exceptional cases the disease is permanently arrested." Birley and Dudgeon (1921), in a paper dealing with the clinical and experimental aspects of the disease, concluded, "Patients in whom the initial disturbance is relatively sudden may remain in perfect health for months or years at a time. How long this immunity can last we are not in a position to say but in view of the fact that the existence of a non-progressive group is generally admitted, together with the circumstances that the initial stages of the disease are frequently overlooked or wrongly diagnosed, it seems possible at any rate that more cases than is commonly supposed recover from their early lesion and remain well permanently." In 1936, Brain, in summarizing his views on prognosis, wrote "If a remission may last thirty years why not for a lifetime? The overwhelming number of patients in whom the disease is progressive should not blind us to the probability that the continuous series from the most acute to the most benign forms extends further to include those in whom a first attack is never followed by another." This last group is represented in the present series by the 23 patients who after the first year have not so far relapsed. Either these cases represent a *benign* form of multiple sclerosis or alternatively the original symptoms were those of an acute disseminated encephalomyelitis (A.D.E.M.). The thorny question of the relationship of these two conditions has been the subject of much discussion over the past thirty years, some contending that they represent two distinct types of demyelinating process, others favouring the so-

XUM

called "unitary" theory, first put forward by Pette (1928) who, in discussing the various forms of encephalomyelitis which became more frequent following the First World War, expressed the view that they bore a close relationship to multiple sclerosis. In discussing acute multiple sclerosis and perivenous diffuse encephalomyelitis, he and his colleagues have recently (1959) reaffirmed that a differential diagnosis on clinical grounds alone is often impossible. Histologically, in acute multiple sclerosis, the association of characteristics plaques and fresh foci of perivenous encephalomyelitis show, in their opinion, that there are no fundamental differences between these two conditions. They refer to the fact that not infrequently a disorder initially diagnosed as parainfectious encephalomyelitis on clinical grounds may later develop a picture of multiple sclerosis. Support for the "unitary" theory has come from Ferraro (1944, 1958) and recently from Miller and Schapira (1959).

Those who oppose the unitary theory do so for two main reasons, first because of the extreme rarity with which the post vaccinal and post exanthematous forms of A.D.E.M. are followed by multiple sclerosis and secondly because in their view important differences do exist in the histological changes in the two conditions. These were discussed by van Bogaert in 1950 and quite recently by Lumsden (1961) in a critical analysis of a paper by Uchimura and Shiraki (1957) based on the pathological findings in 9 fatal cases of A.D.E.M. following anti-rabic vaccination.

With regard to so called "primary" or "spontaneous" A.D.E.M. there would now be general agreement that clinically no clear distinction can be drawn between it and multiple sclerosis in its acute form; indeed there must be considerable doubt as to its existence as a clinical entity. A proportion of such cases, as van Bogaert has pointed out (1950), are examples of perivenous encephalomyelitis, similar in all respects to that following the infectious fevers. As to the remainder, some run a course typical of multiple sclerosis while others remain well.

To return to the present series, in one case A.D.E.M. was the alternative diagnosis to multiple sclerosis while a second might have merited the former label. With regard to the remaining case histories in the "unrestricted" group it is difficult in retrospect to visualize an original diagnosis other than multiple sclerosis (modified in some with a qualifying adjective). The failure to relapse in a proportion of these cases does not appear to be an adequate reason for invalidating the diagnosis, since on the basis of the current view that an immunological disturbance is the probable cause of multiple sclerosis, it follows that the individual tempo and outcome of that disturbance must vary within wide limits. Accordingly it seems permissible to put forward a classification based on this fact.

(1) The *malignant* form: resistance to the disease is low, relapses are severe and frequently leading to death in a few months or years.

(2) The *chronic* form: This embraces the majority of cases. The relapse rate and degree of disability are extremely variable but there is a tendency to progression after the first few years, or exceptionally from the onset, with increasing disability and usually premature death.

(3) The *benign* form: The initial attack may be slight or severe but recovery is good, relapses mild and infrequent, or even absent, with the possibility of permanent cure.

The fate of many of those patients classified as "unrestricted" in the present series must be uncertain for some years by reason of the moderate length of follow-up. However, it can be anticipated that a proportion, including especially those with a negligible relapse rate and a long history, will remain permanently well. Three consequences follow the recognition of a "benign" form of multiple sclerosis. First, the gloomy prognosis that is foreshadowed by this diagnosis must be modified. Secondly, a more positive attitude must be taken towards the question of treatment. If, in a significant proportion of patients, resistance is high, it seems possible that in some others a more prolonged period of rest and after care in the early stage of the disease might beneficially influence the subsequent course of the disease. Lastly, for those who conduct therapeutic trials in multiple sclerosis, existing difficulties are increased.

Summary and Conclusions

(1) Unless a specific laboratory test becomes available, the diagnosis of multiple sclerosis must continue to rest on the clinical findings. Lack of agreement on the necessary criteria proves a handicap in comparing the results of group research.

(2) The present study is based on a prospective follow-up of 241 patients who attended the Neurological Department of the Middlesex Hospital, London, and in whom the original diagnosis was multiple (disseminated) sclerosis. The series was limited to those patients whose disease began between January 1930 and December 1949 and who were seen during the first three years of the disease. The follow-up terminated in November–December 1959.

(3) Data are given regarding the methods used in the follow-up and in the grading of patients according to the degree of disability.

(4) The three diagnostic categories, Definite, Probable and Possible are defined.

(5) In analysing the final results cases were classified as Dead, 83 patients, Disabled, 80 patients, and Unrestricted, 78 patients.

(6) The results of an analysis of the degree of disability in 80 patients show that of those followed up for fifteen and twenty years a significant proportion were not severely incapacitated.

(7) 78 patients, or roughly one-third of the whole series, at the end

XUM

of the follow-up period were without restriction for normal employment and domestic life but were not necessarily symptom-free. In 46 of these patients the diagnosis was "definite," in 20 "probable" and in 12 "possible." With the exception of 4 patients, those in the first two categories were personally examined at the end of 1959.

(8) 23 patients had no relapse after the first year; 14 of these were classified as "probable" and 9 as "possible." In the remaining 55 patients the average annual relapse rate was at its height in the first two years. Between the third and tenth years the rate fell by two-thirds and after the tenth year it further declined.

(9) The incidence of lower limb weakness, as an initial symptom, in the Dead and Disabled groups was roughly double that in the Unrestricted group, whereas unsteadiness in walking (of cerebellar origin) occurred with approximately the same frequency in the three groups.

(10) The results are given of an analysis of pyramidal signs at various stages of the disease in the Unrestricted group of patients.

(11) In 163 patients comprising the Dead and Disabled, the incidence of unilateral or bilateral extensor plantar responses within three years of onset was 70 per cent compared with the figure of 38 per cent in the Unrestricted group. Of the 83 patients who have died, 54 per cent were moderately or severely paraplegic when first seen.

(12) Cerebellar signs were present in 41 per cent of patients in the Dead and Disabled groups at the initial examination, contrasting with 14 per cent in those patients in the Unrestricted group.

(13) These findings suggest that if a patient within three years of the onset of multiple sclerosis shows signs of an established paraplegia, especially when accompanied by cerebellar ataxia, disability is likely to increase in severity, subsequent relapses enhancing this risk and increasing the probability of premature death.

(14) The exceptionally high percentage of patients in this series in whom the disease appears to be running a mild course can partly be explained by the inclusion of 23 among the Probable and Possible cases who, so far, have not relapsed after the first year. Reasons are given for the belief that these and the remaining cases in the Unrestricted group represent a *benign* form of multiple sclerosis. The alternative possibility that a "primary" or "spontaneous" form of acute disseminated encephalomyelitis accounted for the original symptoms only arose in 2 cases. Furthermore, doubt is expressed as to the existence of this form of acute disseminated encephalomyelitis as a clinical entity.

(15) The main characteristics of the *benign* form of multiple sclerosis appear to be as follows—first, an acute type of onset affecting optic nerve, brain-stem or dorsal columns of the spinal cord; secondly, a low relapse rate, particularly after the second year and thirdly when relapses do occur their effect on pyramidal and cerebellar pathways is relatively slight and transient. If, in a particular patient, these conditions still hold

after the disease has been in existence for ten years, the prognosis is quite favourable, bearing in mind that exceptionally a severe relapse leading to disability may occur late in the disease.

(16) A brief reference is made to treatment. Hospitalization was aimed at especially in the early case. In those patients in whom the disease subsequently ran a benign course, half of them were admitted to hospital in the first year of the disease. The period of rest in the early active stage of the disease, the advice given as to future mode of living and the stress laid on rest in bed during a relapse may have played a part in modifying the course of the disease. Treatment with intravenous novarsenobillon, usually preceded by artificial fever, and followed by liquor arsenicalis between the courses, was carried out in 46 patients for a minimum of two years. Statistically the value of this treatment is not apparent although the possibility cannot be dismissed that in some patients it may have contributed to the subsequent freedom from serious relapse.

Acknowledgments

I wish to thank Professor Alan Kekwick and the members of the Clinical Research Committee of the Middlesex Hospital for facilities provided at the Institute of Clinical Research, Mr. T. E. Cowan and his staff in the Records Department, and Miss V. Hughes for secretarial help. Without the willing co-operation of many general practitioners this study would not have been possible and to them I am grateful. Professor P. C. Cloake and Dr. Honor Smith read the manuscript and I wish to thank them for constructive criticism.

REFERENCES

Allison, R. S. (1950) *Brain*, **73**, 103.
——, and Miller, J. H. D. (1954) *Ulster med. J.*, **23**, Suppl. 2.
Birley, J. L., and Dudgeon, L. S. (1921) *Brain*, **44**, 150.
Bogaert, L. van (1950) *J. Neuropath.*, **9**, 219.
Brain, W. R. (1936) *Lancet*, **2**, 866.
Bramwell, B. (1917) *Edinb. med. J.*, **18**, 16.
Charcot, J. M. (1872) "Leçons sur les maladies du système nerveux." Paris.
Cloake, P. C. (1946) Humphry Davy Rolleston Lecture: Roy. Coll. Phys., London. "The treatment of disseminated sclerosis by artificial pyrexia and prolonged administration of arsenic" (unpublished).
Ferraro, A. (1944) *Arch. Neurol. Psych.*, **25**, 723.
—— (1958) *J. neuropath.*, **17**, 278.
Lumsden, C. E. (1961) "Scientific Aspect of Neurology." Ed. H. J. Garland, Edinburgh and London.
Marie, P. (1895) "Lectures on Diseases of the Spinal Cord." London.
McAlpine, D., and Compston, N. (1952) *Quart. J. Med.*, **21**, 135.
Miller, H., and Schapira, K. (1959) *Brit. med. J.*, **1**, 737 and 811.
Müller, R. (1949) *Acta med. scand.*, Suppl. 222.
Pette, E., Pette, H., and Bauer, H. (1959) *Dtsch. med. Wschr.*, **84**, 2061.
Pette, H. (1928) *Dtsch. Z. Nervenheilk.*, **105**, 76.
Uchimura, I., and Shiraki, H. (1957) *J. Neuropath.*, **16**, 139.

XUM

THE DIAGNOSTIC VALUE OF THE CHEMICAL EXAMINATION OF CEREBRAL CYST FLUIDS

BY

H. B. SZLIWOWSKI AND J. N. CUMINGS

(From the Dept. of Chemical Pathology, Institute of Neurology, The National Hospital for Nervous Disease, Queen Square, London, W.C.1)

IN 1950 one of us (Cumings, 1950) recorded findings in the chemical examination of cerebral cyst fluids in association with cerebral tumours, and suggested that it might be possible from the results to indicate the degree of malignancy, or in some cases, even the nature of the tumour in association with the cyst. Following this a further series has been examined and certain criteria were determined upon which over the past few years have been used in diagnosis.

This paper records a comparison of the diagnoses made by histological and by chemical methods in a series of such cases. Recently, a further number of cerebral cyst fluids have been examined for various enzymes as well as by the other routine procedures.

Methods

The cyst fluids were examined for total protein together with the electrophoretic pattern, alkaline phosphatase, and cholesterol, by the methods used previously (Cumings, 1950). The enzymes estimated with the methods employed are glutamic oxalacetic transaminase (G.O.T.) (King, 1958), lactic dehydrogenase (L.D.H.) (Wróblewski and LaDue, 1955), phosphohexose isomerase (Bodansky, 1954) and aldolase (Sibley and Lehninger, 1949).

Criteria for Diagnosis

Variations in protein, alkaline phosphatase and cholesterol have been found in the various cyst fluids and the following are the standards that were used for the diagnosis of the degree of malignancy or the nature of the tumour.

Astrocytoma of Cerebrum

	Grade 1	*Grade* 2	*Grade* 3	*Grade* 4
Total protein (g./100 ml.)	up to 3·0	up to 3·5	up to 4·5	4·0–6·0
Cholesterol (mg./100 ml.)	about 120	100–150	130–170	140–200
Alkaline phosphatase (units/100 ml.)	1–2	1–3	3–4	3–8

Secondary Carcinoma

Total protein (g./100 ml.)	.. 4·0–6·0
Cholesterol (mg./100 ml.)	.. 130–200
Alkaline phosphatase (units/100 ml.)	.. 3+

Some of the fluids contained more than 8 units per 100 ml. of alkaline phosphatase and these were always derived from a secondary carcinoma, especially when the primary was in the intestinal tract, kidney and ovary.

Cerebellar Tumours

	Hæmangioblastoma	*Astrocytoma*
Total protein (g./100 ml.)	up to 3·0	over 2·5
Cholesterol (mg./100 ml.)	up to 50	over 100
Alkaline phosphatase (units/100 ml.)	up to 1·0	over 1·0

Suprapituitary Tumours

Often high figures were obtained for all three substances; a protein content of over 4·0 grammes per 100 ml., cholesterol of over 150 mg. per 100 ml., and alkaline phosphatase of between 4 and 15 units per 100 ml.

It is important in the consideration of the degree of malignancy of a tumour, or in the differential diagnosis of the tumour, to consider the results as a whole rather than to use the figures for any single substance. It must also be remembered that the fluid obtained from a cyst which had previously been evacuated, may differ in composition from the original.

Results

A total of 214 cyst fluids have been examined; the tumours taken at operation from these patients were diagnosed histologically on 167 occasions. Of the remaining 47 patients, confirmation was obtained at some time in 17 cases. The histological diagnoses were obtained after all these fluids had been examined and the diagnosis as indicated by the chemical examinations had been reported.

Tables I–V show the results obtained in the fluid examinations in association with tumours verified histologically at operation.

Table VI shows the diagnoses arrived at by chemical examination in 47 cyst fluids where the tumour was not initially verified at operation. Of these cases post-mortem confirmed the nature of a cerebral astrocytoma on five occasions and also of one secondary carcinoma. A second or later biopsy confirmed the diagnosis of astrocytoma on six other occasions, while the surgeon by macroscopic appearance verified the five cases of suprapituitary cysts, even though no histological verification was obtained.

XUM

TABLE I.—CYST FLUIDS IN CEREBRAL TUMOURS

Type of tumour	*Classification of tumour*	
	By histology	*By chemistry*
Astrocytoma grade 1 ..	6	3
„ 2 ..	7	33
„ 3 ..	58	44
„ 4 ..	18	9
Secondary carcinoma ..	22	9
		(and 5 others were graded as highly malignant)

TABLE II.—CYST FLUIDS IN CEREBELLAR TUMOURS

Type of tumour	*Classification of tumour*	
	By histology	*By chemistry*
Hæmangioblastoma	9	10
Astrocytoma grade 1 ..	4	0
„ 2 ..	2	5
„ 3 ..	2	3
„ 4 ..	0	1
Secondary carcinoma ..	6	3
		(and 3 others were graded as malignant grade 3)

TABLE III.—PITUITARY TUMOURS

Type of tumour	*Classification of tumour*	
	By histology	*By chemistry*
Suprapituitary	9	14
Chromophobe adenoma ..	6	—

TABLE IV.—RESULTS OF CHEMICAL EXAMINATION OF FLUIDS FROM NEUROFIBROMA

Name	*Total protein g./100 ml.*	*Cholesterol mg./100 ml.*	*Alkaline phosphatase units/100 ml.*
W. H.	1·0	32	0
L. S.	2·0	82	1·0
H. P.	2·5	145	1·0
C. M.	2·9	150	2·0
S. H.	3·0	140	1·0
D. L.	3·7	158	2·0
H. H.	3·84	—	—
A. LeM.	4·16	152	3·4
J. C.	4·5	205	—
M. W.	5·0	110	4·5
B. M.	5·1	116	2·2
J. C.	5·9	312	9·0

TABLE V.—RESULTS OF CHEMICAL EXAMINATION OF FLUIDS FROM MENINGIOMA

Name	*Total protein g./100 ml.*	*Cholesterol mg./100 ml.*	*Alkaline phosphatase units/100 ml.*
M. D.	4·0	50	1·0
F. P.	4·24	—	3·0
J. W.	4·56	181	2·2
M. C.	5·24	196	2·3
A. F.	5·3	100	3·0
C. R.	7·0	150	6·0

TABLE VI.—CYST FLUIDS WITH NO HISTOLOGICAL VERIFICATION AT BIOPSY

Site of tumour	*Chemical diagnosis*	*Number*
Cerebrum	Astrocytoma grade 1	0
	,, 2	7
	,, 3	19
	,, 4	5
	Secondary carcinoma	7
Cerebellar	Hæmangioblastoma	2
	Astrocytoma grade 2	2
Pituitary	Suprapituitary	5

Post-mortem confirmed nature of cerebral astrocytoma on 5 occasions; a second or later biopsy confirmed diagnosis on 6 occasions, while the operation findings confirmed 5 cases of suprapituitary cysts. One cerebral secondary carcinoma was confirmed at post-mortem.

In general, there is a reasonable degree of agreement between the diagnosis arrived at by chemistry and by histology. It is obvious that histology tends to grade cerebral astrocytoma more highly than chemistry but this is possibly because the criteria used were not adequate. An adjustment should be made and the appropriate figures for grade 2 should read—protein up to 3·0 grammes per 100 ml., cholesterol 100–125 mg. per 100 ml., alkaline phosphatase 1–3 units per 100 ml., and grade 3 protein 3–4·5 grammes per 100 ml., cholesterol 120–160 mg. per 100 ml., alkaline phosphatase 2–4 units per 100 ml. With cerebellar tumours the reverse is true as histology usually suggested a lower degree of malignancy than did the chemical findings.

The figures obtained for the composition of the cyst fluids in cases of neurofibroma and meningioma are interesting but not really instructive.

Enzymes

A further series of 57 cases have been examined by the standard methods together with determinations of the various enzymes.

Table VII shows the results that have been obtained in the 40 of these

XUM

TABLE VII.—ENZYME CONTENTS OF CEREBRAL CYST FLUIDS

Name	Classification of tumour: By histology	By chemistry	Total protein	Alkaline phosphatase	Cholesterol	Glutamic oxalacetic transaminase	Lactic dehydrogenase	Aldolase	Isomerase
L. T.	Cerebral astrocytoma grade 2	Grade 3	5·7	1·7	130	230	143		40
A. B.	" " " "	" "	3·5	1·7	200	75	3600	204	
D. S.	" " " "	Low grade	1·4	1·8	31	275	270		12
E. C.	Cerebral astrocytoma grade 3	Grade 3	5·5	5·2	174	2060	19950		4300
S. C.	" " " "	secondary carcinoma	6·2	11·0	212	249	6320		2200
T. C.	" " " "	Grade 2–3	3·1	2·8	154	210	796		947
R. F.	" " " "	Grade 3	7·2	1·0	280	177	3330		960
J. E.	" " " "	Grade 2–3	4·0	1·0	144		1026		
F. W.	" " " "	Grade 3	5·0	4·1	185	297	9125		
G. R.	" " " "	—	0·6	0·1	8	60	130	4	
G. W.	" " " "	Grade 3	4·7	1·1	610	286	920	40	
E. B.	" " " "	" "	5·2	1·3	130	215	5400	250	
D. C.	" " " "	" "	6·0	0·8	160	420	14500	75	
E. F.	" " " "	" "	4·3	0·6	140	380	6500	130	
L. T.	Cerebral astrocytoma grade 4	Grade 3	5·0	1·6	120	99	533		193
P. W.	" " " "	Grade 3–4	5·2	3·5	200	405	150		1175
J. B.	" " " "	Grade 3	5·4	3·3	185	308	10000	340	
M. H.	" " " "	—	1·3	0·4	0	400	5000	90	
J. W.	" " " "	Grade 3	5·6	1·7	110	770	11500	100	
G. R.	" " " "	Grade 2–3	3·7	3·9	125	199	8000		
P. S.	Cerebellar Astrocytoma	—	3·3	1·8	100	259	195		8
D. B.	" "	Low grade glioma	2·8	1·4	66	250	340	4	
C. H.	" "	Grade 2	2·8	1·4	115	162	100		11
J. G.	Cerebellar hæmangioblastoma	Hæmangioblastoma	3·5	1·0	65	247	210		
W. K.	" "	"	6·2	1·8	90	133	58		56
A. S.	" "	"	2·2	0·2	40	350	200	6·5	
O. B.	" "	Astrocytoma grade 2	5·0	2·3	83	181	136		18
E. O'B.	Cerebellar ependymoma	Grade 3	6·4	2·1	85	140	190	3	
G. F.	Secondary carcinoma	—	4·3	2·1	224	370	95000		
E. C.	" "	Grade 2–3	3·7	5·1	167	75	700		
B. McK.	" "	Grade 3–4	6·3	3·3	100	1490	21000		4160
B. L.	" " (Breast)	Prob. secondary carcinoma	5·0	3·4	200	1900			
E. M.	" " (Lung)	Grade 3	4·5	3·0	105	640	6075		
D. G.	Meningioma	—	1·6	1·4	43	31	11		7
F. G.	"	—	3·2	1·8	45	115	40		
J. C.	Pituitary chromophobe	—	6·3	0·6	170	180	1850	25	
G. B.	Craniopharyngioma	Craniopharyngioma	5·3	14·5	230	164	236		88
G. B.	"	"	6·7	3·7	170	150	630	4	
A. O.	Rathke pouch	—	2·5	1·8	255	170	900		367
A. C.	Epidermoid	—	10·3	0·4	318	105			

Total protein in grammes/100 ml. Alkaline phosphatase in units/100ml. Cholesterol in mg/100 ml. Transaminase in units/100 ml. Lactic dehydrogenase in units/1 ml. Aldolase in units/100 ml. Isomerase in units.

cases in which there is definite histological evidence of the nature of the tumour.

Cerebral astrocytoma grades 3 and 4 and secondary carcinoma, appear to have high contents of G.O.T., L.D.H., and isomerase in most cases but this is not absolutely a constant feature. There is so far a marked difference in isomerase content between the malignant and the non-malignant tumours and this may be a useful diagnostic feature.

Discussion

The results of the examination of cyst fluids for protein, alkaline phosphatase and cholesterol have indicated that in general the diagnosis arrived at by this method agrees quite well with the histological examination. Very few studies on similar lines have been made but Spiegel-Adolf and Wycis (1954) obtained protein levels of 0·17 to 7·2 grammes per 100 ml., for various tumours and later they reported figures of 2·82 to 6·86 grammes per 100 ml. in 14 tumours (1957), while Ectors (1959) found that the protein level in cysts associated with both astrocytoma and hæmangioblastoma of the cerebellum averaged 4·0 grammes per 100 ml.

Ledinsky and Štěpăn (1957) estimated levels of cholesterol in 10 cyst fluids associated with brain tumours. The levels they found were higher than those reported here for in a cerebral astrocytoma grade 1, a figure of 261 mg. per 100 ml., was obtained, while for tumours comparable to our grades 3 and 4, figures of 93, 144 and 249 mg. per 100 ml., were found. One cerebellar hæmangioblastoma and one astrocytoma grade 1 of the cerebellum gave figures of 184 and 120 mg. per 100 ml., respectively. These figures are on the whole surprisingly high and are considerably greater than any that we have obtained for comparable tumours.

Considering now the results in Table VII, it must first be mentioned that there are two unusual results. One patient, S. C., with an astrocytoma grade 3, was diagnosed as a secondary carcinoma as a result of the high alkaline phosphatase. This is the only occasion in which such a finding has been seen and suggests the possibility of an error in the estimation. The patient O. B., who had a cerebellar hæmangioblastoma, was misdiagnosed chemically because it was not known at the time of the examination that the cyst had been previously evacuated and the fluid examined this time was from a repeat tap. As we have found on previous occasions, the results obtained at a repeat examination, do not parallel the findings on the first examination.

The enzyme studies reported show a definite tendency for raised levels of G.O.T., and L.D.H., to be found in the more malignant tumours. There is, however, little difference between the values found for these two enzymes in the two main types of cerebellar tumour examined, while the figures for cysts associated with a cerebellar ependymoma and with

meningioma are very considerably lower than in any other type of cyst. Green *et al.* (1958) in a single case of cerebral astrocytoma found in the cyst fluid a level of G.O.T. of 713μ M of oxalacetate produced per hour per 100 ml. of fluid at 37° C., and of L.D.H., of 16306μ M of lactate produced per hour per 100 ml. of fluid at 37° C. They comment on the very much greater level of L.D.H. as compared with G.O.T., with which our findings are in agreement. A number of estimations have been made on the content of these two enzymes in the cerebrospinal fluid in cases of cerebral tumour (Myerson *et al.*, 1957; Katzman *et al.*, 1957; Green *et al.*, 1957; Fleisher *et al.*, 1957; and Fieschi and Soriani, 1957) and in all cases of primary brain tumour figures about normal have been obtained. Wróblewski *et al.* (1957) however, found raised levels of L.D.H., in the cerebrospinal fluid in cases of secondary carcinoma of the brain, while Green *et al.* (1958) found raised levels in the cerebrospinal fluids in all primary or metastatic tumours of the brain.

The number of aldolase estimations that were made is very small and not representative, mainly because it was felt that the results were not likely to be of any diagnostic value and so these enzyme estimations were discontinued.

The estimation of phosphohexose isomerase yielded interesting results for despite relatively few numbers. it is clear that high figures are obtained in the more malignant glioma and in secondary carcinoma, even though they do not distinguish the one from the other. It would seem that this examination may be of considerable value in the determination of the degree of malignancy.

Thompson *et al.* (1959) found that the level of this enzyme was higher in the cerebrospinal fluid in 21 out of 33 patients with neoplastic cerebral tumours, whereas in benign tumours there was no such increase apart from one single case which was that of an 8th nerve neurofibroma.

There is little doubt that the chemical examination of the cyst fluids together with an estimation of L.D.H., and isomerase will yield valuable diagnostic results, which will be of considerable importance when tumour tissue cannot be obtained.

Summary

A comparison between the results of the chemical analysis of 214 cyst fluids associated with tumours of the brain and the histological diagnosis is recorded.

Studies on the contents of some enzymes in 57 cystic fluids have been made, and raised quantities of L.D.H., and phosphohexose isomerase are shown to be present in malignant tumours.

It is suggested that by means of selected chemical examinations useful evidences of the nature and degree of malignancy can be obtained.

Our very grateful thanks are recorded to Professor W. Blackwood and Professor T. Crawford for the histological diagnoses and to Mr. Harvey Jackson, F.R.C.S., and Mr. Wylie McKissock, F.R.C.S., for their helpful assistance in obtaining the cyst fluids.

One of us (H. B. S.) also wishes to thank the Ministry of Public Instruction, Belgium, and the International Rotary Club of Brussels for personal grants.

REFERENCES

BODANSKY, O. (1954) *Cancer, Philad.*, **7,** 1191.
CUMINGS, J. N. (1950) *Brain*, **73,** 244.
ECTORS, L. (1959) *Acta chir. belg.*, **58,** 449.
FIESCHI, C., and SORIANI, S. (1957) *Boll. Soc. ital. Biol. sper.*, **33,** 1445.
FLEISHER, G. A., WAKIM, K. G., and GOLDSTEIN, N. P. (1957) *Proc. Mayo Clin.*, **32,** 188.
GREEN, J. B., OLDEWURTEL, H. A., O'DOHERTY, D. S., FORSTER, F. M. (1958) *A.M.A. Arch. Neurol. Psychiat.*, **80,** 148.
—— —— —— —— and SANCHEZ-LONGO, L. P. (1957) *Neurology*, **7,** 313.
KATZMAN, R., FISHMAN, R. A., and GOLDENSOHN, E. S. (1957) *Neurology*, **7,** 853.
KING, J. (1958) *J. med. Lab. Tech.*, **15,** 17.
LEDINSKY, Q., and ŠTĚPÁN, J. (1957) *Zbl. Neurochir.*, **17,** 378.
MYERSON, R. M., HURWITZ, J. K., and SALL, T. (1957) *New Engl. J. Med.*, **257,** 273.
SIBLEY, J. A., and LEHNINGER, A. L. (1949) *J. biol. Chem.*, **177,** 859.
SPIEGEL-ADOLF, M., and WYCIS, H. T. (1954) *J. Neuropath.*, **13,** 601.
—— —— (1957) *J. Neuropath.*, **16,** 404.
THOMPSON, H. G., Jr., HIRSCHBERG, E., OSNOS, M., and GELLHORN, A. (1959) *Neurology*, **9,** 545.
WRÓBLEWSKI, F., and LADUE, J. S. (1955) *Proc. Soc. exp, Biol.*, **90,** 210.
—— DECKER, B., and WRÓBLEWSKI, R. (1957) *Amer. J. clin. Path.*, **28,** 269.

CENTRAL DEMYELINATION OF THE CORPUS CALLOSUM (MARCHIAFAVA-BIGNAMI DISEASE)

With Report of a Second Case in Great Britain

BY

R. IRONSIDE, FRANCES D. BOSANQUET AND W. H. McMENEMEY

Maida Vale Hospital for Nervous Diseases, London, W.9

Introduction

The essential lesion of this rare condition is a central demyelination, sometimes amounting to necrosis, of the corpus callosum. It is found almost exclusively in alcoholic males, and is associated with a terminal illness in which speech disorder and mental deterioration are prominent early signs, with stupor, convulsions, rigidity and bilateral neurological signs appearing later. The pathological process is probably subacute although the clinical signs may appear with great suddenness, after years of excessive alcohol-drinking.

We record here the second case to be described in Great Britain and in an English native, the patient being a male addicted to beer and spirits. The first case in this country was recorded by McLardy (1951). As British neurological literature contains no comprehensive review of the condition we have surveyed the literature from the beginning of the century. Problems raised by the striking and characteristic lesion, in which degeneration is confined to the central zone of the corpus callosum, and the possible ætiology are discussed.

Reviews are available from the Argentine (Orlando, 1952), Austria (Seitelberger and Berner, 1955), French Switzerland (Jéquier and Wildi, 1956) and France (Gruner, 1956) while an Italian account of the disease by Fittipaldi (1937) summarizes all the cases up to that date. The earlier papers in English are those of King and Meehan (1936), Nielsen and Courville (1943), Merritt and Weisman (1945) all in U.S.A., and McLardy (1951) in U.K. Marchiafava's communication to the Neurological Section of the Royal Society of Medicine, London (1933), brought the condition to the notice of many for the first time. To our knowledge it has not been diagnosed during life but it should certainly be borne in mind when an alcoholic male rapidly develops dementia with speech disorder, convulsions and bilateral rigidity or pyramidal signs.

Case Report

M. V., 37092, a 52-year-old lift attendant, was born in County Durham of English parents and for many years served at sea in the Far East and in South American waters. From early life he was a heavy drinker. He had one daughter who is alive and well.

Previous health.—At the age of 34 years he was treated effectively for a primary chancre. At the age of 36 and while at sea he sustained during an air attack a superficial shrapnel wound of the muscles of the back and severe burns of both legs; for nineteen months he was in hospital at Montevideo and was then sent home. Four years later he was invalided from the Service after many operations for skin-grafting had been carried out.

Family history.—One brother, said to have been an alcoholic, died suddenly at the age of 28 years.

Habits.—He was reputed to have drunk ten to fifteen pints or more of stout or draught bitter beer daily, and a variable amount of whisky and rum, but no wine. There is no history of his taking methylated spirits.

Eight years before his death, after separation from his wife, living in lodgings and fending for himself, he began to eat poorly and to drink more heavily. His daughter stated that he never ate breakfast nor any meat. "He thought the cost of food was terrible," she said, "but he didn't seem to mind the price of beer."

He was right-handed.

History of illness.—For some eighteen months before he died he had earned the reputation of being mean and querulous, intolerant of noise and children, absent-minded and making stupid mistakes. He had lost his sense of smell, and so was afraid to use the gas cooker. He also complained of failing vision.

One day in a bar he suddenly became temporarily dysphasic but shortly before was stated to have babbled somewhat incoherently. Four days later, on September 24, 1956, he was discovered unconscious beside his bed and taken to hospital where he was found to be in a conscious state but with gross expressive dysphasia, some degree of neck rigidity and extensor plantar responses. The following day he had a right-sided Jacksonian attack which was followed by a generalized fit, each seizure lasting about ten minutes. A slight residual right hemiparesis became apparent. The spinal fluid pressure was 115 mm. with 5 lymphocytes per cmm., protein of 20 mg. per cent, Lange and W.R. negative. He was seen by one of us (R. I.) and transferred to Maida Vale Hospital on September 29, conscious, open-eyed and able to understand and obey simple commands: he had however severe expressive dysphasia. The fundi showed slight arteriosclerotic changes (grade II) but the optic discs were normal. The visual fields were full to "menace" tests. The pupils were equal, circular and central and reacted normally, and the ocular movements were full. There was no ptosis. The other cranial nerves were normal except for bilateral anosmia. There was marked spasticity of the right arm and slightly increased tone in both lower limbs. The left arm moved normally. There was no response to painful stimuli applied to the right arm, but there was normal response in the left arm and lower limbs. At times the upper limbs were flexed and the lower limbs extended as in decerebration. All the tendon reflexes were exaggerated. Both plantar responses were extensor and the abdominal reflexes were absent.

The heart presented no abnormal physical signs and there was no clinical evidence of aortic or peripheral arteriosclerosis. The blood pressure was 140/80. The liver was not palpable. The urine had a specific gravity of 1025, was acid and gave a heavy cloud of protein but no reducing substance. The blood revealed Hb 103 per cent; W.B.C. 10,600 per cmm. with a normal differential count; E.S.R. 95 mm. (Wintrobe)—thought at the time to be possibly due to a chest infection; Wassermann, Meinicke and

XUM

Kahn reactions all negative. The blood urea was 50 mg. per 100 ml. and the serum protein 5·8 grammes per 100 ml. Serum electrophoresis showed an increase in alpha$_2$ and beta globulins; the albumen was decreased. Pyruvate metabolism was not investigated. Radiographs of the skull were normal; those of the chest showed consolidation of the lower lobe of the left lung. The EEG was abnormal, but no satisfactory record could be obtained as the patient was unable to co-operate. Delta potentials (2–$\frac{1}{4}$ c/s) were recorded from all regions, with amplitudes of the order of 50–100 μV. Some bursts of theta activity (4–6 c/s) at 50 μV were recorded in the temporal regions. The conclusion was reached that there was no consistent asymmetry and no evidence of focal abnormality (Dr. S. Nevin).

Soon after admission his conscious state deteriorated, he could not obey commands and he was no longer able to co-operate in examination. Within three days he had become stuporose with extensor spasms of the legs and of both upper limbs. His temperature rose to 104° F. He was given massive doses of thiamin administered parenterally (250 mg. daily for a week) and chloramphenicol but died of bronchopneumonia seventeen days after the onset of his acute illness.

At first the physical signs had suggested a left-sided frontal or temporal subcortical lesion, but later the picture had been one of stupor with partial decerebration. The diagnoses considered during life were (1) an intracerebral vascular accident, (2) intracranial frontal tumour in an alcoholic patient, and (3) Wernicke's encephalopathy. The possibility was considered of cerebral anoxia complicating an existing pathological lesion, as it was known that for some hours he had lain unconscious on the floor.

Necropsy performed thirty-three hours after death, revealed the body of a somewhat emaciated man, looking older than his years. The skin appeared to be in good condition apart from the scarring of the legs (war burns).

The *general examination* revealed a left lung adherent over the apex with long-standing bronchopneumonia in which the multiple areas of consolidation appeared unusually discrete. Histologically, there were in the apical lesion occasional giant cells lying in relation to small areas of caseation: this was believed to be an active and spreading area of fibrocaseous tuberculosis. In addition there was widespread purulent broncho-pneumonia on both sides. There was no atrophy of the tongue papillæ and no cirrhosis of the liver. The heart weighed 280 grammes and the amount of atheroma in the aorta, great vessels of the neck and coronary arteries was negligible. There was no intracranial infection or hæmorrhage, and the skull and dura mater were normal.

The *brain* weighed 1,240 grammes and was a little shrunken with some widening of the sulci, particularly in the frontal lobes. The leptomeninges showed a slight generalized thickening but there was no evidence of active meningitis. Blood vessels of the circle of Willis and elsewhere were healthy and there was no evidence of venous thrombosis.

Coronal sections through the fixed brain confirmed the mild generalized atrophy, most marked in the frontal lobes, associated with slight enlargement of the ventricles. The striking feature however was the clearly demarcated softening of the central fibres of the corpus callosum extending throughout its whole length and, except posteriorly, more or less symmetrically across the mid-line (fig. 1, Plate XXV). There was no overall reduction in depth of the corpus callosum and the "necrotic" middle third which varied from 3 to 5 mm. in depth and extended on average 35 mm. from side to side lay sandwiched between two apparently healthy layers of fibres. In the centre of the corpus callosum the softened part was faintly brown, while at both the genu and splenium it was whiter and firmer. Macroscopic softening was confined to the corpus callosum (fig. 2) except posteriorly on the right where two small patches were present in the white matter adjacent to the posterior horn of the ventricle (fig. 3). The optic chiasma and optic tracts appeared normal. There was, however, some congestion of

the cerebral white matter generally and of the cortex in the right parietal region. The anterior cerebral and other main arteries and also the veins, were patent.

In paraffin sections the softening appeared almost complete with a clear-cut edge, like an infarct, and packed with fat-laden macrophages (fig. 4). These cells were more numerous around the edge of the softening and were noticeably fewer in the centre (fig. 5). Occasional single myelinated fibres, or small islands of myelinated fibres, tended however to persist even in the centre of the softening (fig. 6) suggesting that the lesion was more patchy than appeared at first sight. Bielschowsky and Glees stains (fig. 7) showed that some nerve fibres were preserved even in what had appeared to be completely degenerated areas. Swellings on the nerve fibres and fragmentation were seen but they were not a marked feature. Loss of myelin was indeed more pronounced than the destruction of nerve fibres. Astrocytes were present within the softening but in very small numbers, fewer in fact than in the surrounding white matter. There was no laying down of glial fibres as is seen in the lesions of multiple sclerosis. Apart from cytoplasmic swelling the oligodendrocytes in the vicinity of the softenings appeared normal.

Blood vessels within the lesion were relatively prominent on account of loss of other tissues, but it is doubtful if there was genuine proliferation. An occasional peripherally placed vessel was surrounded by lymphocytes, but on the whole cuffing was hardly noticeable. No thrombi were found.

The small softenings adjacent to the posterior ventricular horns were similar to the main area, with the same sharp edge (fig. 3): they may have been outlying points of the main softening but the fact that they were stuffed with fat granule cells suggested that they were rather more recent. This and the difference in colour and texture of the main softening at each end (genu and splenium) supports the possibility that there had been a number of pathological episodes rather than one.

Marchi, fat and myelin stains revealed no degeneration of the central white matter of the cerebral hemispheres, nor of the anterior commissure, the optic tracts, nor the cerebellar peduncles. The corpora mammillaria were normal. The cerebral cortex generally showed slight loss of nerve cells and some pairing of astrocytic nuclei more especially in layers 3, 4 and 5. In one place in the superior frontal convolution as many as seven astrocytic nuclei were seen together. Alzheimer type II cells were not seen. The nerve cells seemed mostly healthy but on occasions there was irregularity of the nuclear membrane and some densification of the chromatin. There was no noticeable accentuation of this degenerative process in the second temporal convolution and there was no appreciable loss of cells in the *area pyramidalis subiculi simplex*. In the basal ganglia there was some thickening of the vessels in the putamen and globus pallidus, while in the caudate nucleus and amygdala there was a slight increase in the number of astrocytes; no major degeneration was found. The cerebellum including the vermis showed no loss of Purkinje cells and no excess Bergmann cells; there was however some swelling ("lifting") of the Purkinje cell layer, more especially on the crowns of the folia. The pons, midbrain and medulla were normal apart from a small glial knot in the lateral cuneate nucleus.

Pathological Commentary

The diagnosis was made on the macroscopic appearance of the brain which was evidently similar to the early examples described by Marchiafava and his associates, and subsequently by others. Like the majority of these cases this one showed only central symmetrical myelinolysis of the corpus callosum without other neurological lesions. There was no associated Wernicke's syndrome, and the anterior commissure and optic chiasma

XUM

were intact. Except in relation to the splenium, there were no areas of demyelination elsewhere such as lead some authors to see a resemblance between this disease and multiple sclerosis. In that the myelin was destroyed to a greater degree than the axons it would be fair to say that this was in essence a demyelinating lesion. However, the massed fat granule cells and lack of gliosis were not like the usual multiple sclerosis plaque (though such an appearance may be found in the more rapid demyelinating conditions such as Devic's disease and in the more acute examples of sudanophilic diffuse sclerosis). The lesion appeared superficially to resemble an ischæmic softening and there was some suggestion that it was the result of a number of episodes beginning in the central area and spreading backwards and forwards: it is difficult, however, to correlate this view with what is known of the clinical history. The blood vessels in the brain appeared healthy. In the cerebral cortex and more particularly the frontal cortex, there was slight loss of cells with astrocytic proliferation, but it did not seem possible to correlate this in any way with segmental damage to the callosal axons.

The callosal lesion was so distinctive and so classical of the Marchiafava-Bignami disease that there could be no doubt as to the diagnosis. The only unusual features of the case were the facts that the subject was an Englishman and that he was a drinker of beer rather than of wines or spirits. Apart from the terminal bronchopneumonia the only associated findings were the left apical focus of tuberculosis and the malnutrition.

Anatomical and Physiological Considerations

The corpus callosum appears first in the mammalian brain and it develops *pari passu* with the increase in the importance of the neopallium, reaching its highest development in primates and man. In the brains of monotremes and most marsupials it is lacking (Edinger 1911, Hyman 1942). Racial variations in the size and degree of development of the corpus callosum have been claimed (Ariens Kappers, 1947).

The genu and splenium can be defined in the sixth month of human fœtal life but myelination of the callosal fibres in man is relatively late, appearing for the first time in the second month of post-natal life. The first to become myelinated are the dorsal fibres (Langworthy, 1932). Mingazzini (1922) finds that between the third and seventeenth month of post-natal life the fibres of the intermediate axial layer are less easily stained for myelin and on this apparent late myelinogenesis he attempts to explain the peculiar localization of the Marchiafava-Bignami lesion.

Anatomists, and physiologists using techniques, including electroencephalography and physiological neuronography, have added to our knowledge of the complicated histology of the corpus callosum (Sunderland, 1940; Curtis, 1940; Chang, 1953; Bremer, 1952, 1953, *et al.*, 1955, 1956 *a* and *b*). It appears that the majority of callosal fibres connect association areas in the cortex of the two hemispheres: a few, however, are projection fibres. From the infragranular layers of cortical association areas transverse fibres cross the mid-line and terminate in supragranular layers of the cortex of the opposite hemisphere. 'Through the commissural fibres the activity of one hemisphere can be immediately reflected and reinforced in the opposite hemisphere, and it has been demonstrated experimentally that this co-operative relationship is abolished by interruption of the fibres" (Clark, 1958). Most regions of the cortex send com-

missural fibres to corresponding topographical regions of the opposite hemisphere, but from certain foci in the frontal and parietal area fibres are distributed extensively to the contralateral cortex and through them widespread activity of the opposite hemisphere can be induced by local cortical activity on one side. Bailey and von Bonin (1951), be it noted, estimate the number of transverse fibres as less than 1 per cent of the cortical cells in each hemisphere.

Ramón y Cajal (1911) described bifurcation of callosal fibres and terminal and subcortical collaterals but most observers are now agreed that collaterals are scarce compared with association and projection fibres. Walberg and Brodal (1953) describe a few efferent projection fibres which arise in the motor cortex, cross in the corpus callosum and extend through the pyramid of the opposite side—an observation made first by Sherrington in 1889.

According to Tomasch (1954) the callosal fibres are very small: in fact only about a third as big as those in the pyramidal tracts. Nonmyelinated fibres constitute on the average 40 per cent of the total, but in some areas they amount to as much as 50 per cent, being most numerous in the anterior quarter and least in the splenium.

The longitudinal fibres (striæ callosi) are part of the rhinencephalon and lie superficial to the thin layer of grey matter (indusium) covering the superior callosal surface.

Beevor (1907) held that the arterial supply of the corpus callosum was from the cortical branches of the cerebral arteries. Goldstein (1914) studied the blood supply in the corpus callosum of man and animals, his diagram of the circulation in the former being reproduced by Mingazzini (1922). The rostrum and lamina terminalis are supplied by branches from the anterior communicating and internal carotid arteries. Penetrating branches of the paired callosal arteries (from the anterior cerebrals) nourish most of the genu and body, whilst the splenium is served by arterioles from the posterior cerebral artery.

The earlier studies of callosal function, which were inconclusive, were based on section experiments in animals and the effects of vascular lesions and tumours in man. Much speculation has existed on the part played by the great commissure in integrating sensory cortical fields serving the perception of symbols, images and sounds whether predominantly right or left-sided. Liepmann (1905) and later Liepmann and Maas (1907) studied vascular lesions and formulated the concept that the left (dominant) hemisphere elaborated eupractic patterns of movement which were impressed in the cortex of the minor hemisphere through the corpus callosum, thus attempting to explain left-sided ideo-motor apraxia ("callosal apraxia") seen sometimes after anterior cerebral artery occlusion.

The first studies of tumours of the corpus callosum (Raymond, Lajonne and Lhermitte, 1906; Ironside and Guttmacher, 1929; Alpers, 1936) emphasized a psychical callosal syndrome of a non-specific kind—loss of memory, confusion and character-change, apraxia or dysphasia being mentioned in less than 10 per cent of cases. The mental state of such patients often renders tests for apraxia or aphasia impossible.

Van Wagenen began to perform callosal section on epileptic patients in the hope that the discharge would thus be confined to one hemisphere. It then seemed that it might be possible (Akeleitis, 1942, 1944; Smith and Akeleitis, 1942) to study a small series of patients with such sharply defined lesions, making use of tests for apraxia both before and after operation. They concluded that unless patients had a concomitant hemisphere lesion no dyspraxia could be demonstrated. In some patients with a hemisphere lesion transient motor apraxia and a grasp-reflex appeared after callosal section, and in 2 patients there were odd symptoms which were interpreted as a rivalry between voluntary movements performed with the right and left upper limbs (Akeleitis, 1944).

The results of electro-physiological studies are included in the comprehensive review by Bremer, Brihaye and André-Balisaux (1956). They describe a facilitation of afferent electrical stimuli delivered to the corpus callosum diminished by paralysis or extirpation

XUM

of the cortical area homologous to the one studied. They furnish EEG evidence of interhemispheric transference of afferent sensory impulses.

Myers and Sperry (quoted by Sperry, 1958), using cats, have carried out psychophysiological experiments which suggest that an intact corpus callosum is necessary for the transfer of learned discriminations from one hemisphere to the other. They first isolated nasal half-fields by antero-posterior median section of the optic chiasma. They then found that if one eye is occluded both hemispheres participate in learning visual discriminations, provided that the corpus callosum is intact. If, however, the latter is sectioned, it can be shown that one hemisphere only has participated in the feat of learning, that one in fact corresponding to the eye which has not been occluded. Results of the same kind occur for tactile discrimination in the forepaw of roughness, hardness and shape. Such discriminations learned with one forepaw are found to transfer to the contra-lateral untrained paw in normal cats, but in cats with the callosum sectioned such contralateral transfer fails, and the discrimination has to be relearned from the beginning with the second paw (Stamm and Sperry, quoted by Sperry, 1958).

The Marchiafava-Bignami lesion, although circumscribed, has been of no use in elucidating callosal function partly because of the non-specific character of the clinical picture, and partly because of the irresponsive state of the patients.

Classical Description of the Lesion

Agostino Carducci (1898), a pupil of Marchiafava, in his thesis for Doctorate of the University of Rome recorded the first published case.

S. D., aged 50 years, an Italian peasant, was a chronic alcoholic. Three years previously he had suffered from delirium tremens from which he had appeared to make a good recovery. A bout of depression lasting two weeks heralded his final illness. One night following a domestic upset he experienced a slight loss of consciousness. Next morning (March 1, 1898) he had a right-sided Jacksonian convulsion involving the face, arm and leg with subsequent loss of consciousness. Later in the day and on successive days other fits occurred, each attack usually lasting four to five minutes. Gradually his speech was affected, he became amnesic and although he could still move his limbs and walk he developed a mental type of urinary incontinence. Four days before death he lapsed into coma, his head being turned to the right. The temperature rose to 39·3 C. before death. The urine (s.g. 1018) contained albumen and casts.

At autopsy a soft greyish area was found in the white matter of the brain above the lateral ventricles. It was most intense and extensive in the corpus callosum: anteriorly following the fornix it spread out into the centrum ovale of the frontal region especially on the right [*sic*]. The rest of the brain, except for a diffuse thickening of the arachnoid, was normal. The lungs showed bronchopneumonia and a fibrinous interlobular pleurisy on the right side: the hepatic capsule was thickened especially over the right lobe. On microscopic examination it was noted that the corpus callosum was divided all the way through into well preserved ventral and dorsal layers colouring well with Weigert's stain, and an intermediate pale layer. This middle zone did not appear to have any fibres in its anterior third, while in the middle third, areas of well preserved fibres were suddenly lost in demyelination. The cortex appeared everywhere normal. There was a replacement gliosis in the degenerated area and compound granular corpuscles were seen in parts of the diseased zone where the fibres were best preserved. There were occasional small hæmorrhages. The blood vessels were engorged but their walls were normal, or only slightly thickened, and without perivascular infiltration.

Carducci considered that the lesion was not a systemic one. Because of persistence

of myelin fibres he would not accept the designation of necrosis and believed that as in multiple sclerosis the axis cylinders remained, otherwise one would have found Wallerian degeneration. The possibility of the lesion being due to ischæmic softening was discussed but he remarked that the degenerated area did not correspond to the distribution of any cerebral artery. He finally concluded that the condition was a degeneration analogous to that seen in peripheral neuropathies (e.g. lead poisoning). He could only assume from the clinical history that the cause of degeneration in this case was alcoholism.

Marchiafava and Bignami (1903) based their account on the findings in the brains of three Italian peasants (one was Carducci's case) addicted to drinking heavily of cheap red wine. The change described was a sharply circumscribed greyish degeneration, sometimes cystic, localized to the middle layer of the corpus callosum throughout its whole extent, its border contrasting sharply with the mother-of-pearl whiteness of the normal white substance. The dorsal and ventral laminæ and the striæ of Lancisi were intact. They emphasized the distribution of the lesion, that it was a periaxial demyelination, and that it differed fundamentally from the "polioencephalitis superior" of Wernicke. They stressed chronic alcoholism as the causal factor.

Time has modified in some ways the picture they originally described. Bignami (1907) pointed out that the anterior commissure might also be affected in what he considered to be a systemic degeneration of the commissural bundles between the two hemispheres. With Nazari (1915) he described foci of demyelination in subcortical association bundles also. It was later noticed that it was the genu and the anterior third of the corpus callosum which was most often and most severely involved. Symmetrical areas of necrosis on either side of the mid-line were sometimes described, and it was noted that these had a tendency to coalesce in the mid-line. Symmetrical areas of necrosis were recorded in the middle cerebellar peduncles (Marchiafava, 1913), in the columns of Goll (de Albertis, 1920), and in the optic chiasma (King and Meehan, 1936). Seitelberger and Berner (1955) pointed out that chiasmal lesions could be due to an associated alcoholic neuropathy of the macular bundles. Gruner (1956) and his co-workers have found the Marchiafava-Bignami lesion in "alcoholic encephalopathy" in association with cortical atrophy, Wernicke's syndrome, demyelinating lesions outside of the corpus callosum and systemic degeneration in fibres of other commissures. Three examples of central pontine myelinolysis as an isolated finding in the brains of alcoholics and malnourished patients have been described by Adams, Victor and Mancall (1959).

Mingazzini (1922) laid stress on the distinction between two pathological processes, (1) softening of the corpus callosum which he regarded as a vascular phenomenon, and (2) degeneration which he attributed to focal loss of myelin. Both types of change are found in the Marchiafava-Bignami disease and they are now considered to be no more than varying

XUM

degrees of reaction to the same harmful agent. Courville (1943) stated that vascular changes may be present in the form of hyalinization of the walls of the vessels, swelling of the endothelium and thickening of the adventitia. Increased vascularity of the affected areas has sometimes been observed, but these changes are not present in every case.

Clinical Commentary

Jéquier and Wildi (1956) surveyed 71 case reports.

Of the cases recorded since 1899, we have accepted 88: Carducci (1), 1898; Marchiafava—Bignami (2), 1903; Rossi (2), 1910; Marchiafava—Bignami—Nazari (9), 1911; Giannelli (1), 1912; Demel (1), 1912; Marchiafava (1), 1913; Milani (2), 1914; Marchiafava (1), 1915; Bignami—Nazari (19), 1915; Guizzetti Tommasinelli (1), 1915; de Albertis (1), 1920; Laignel-Lavastine (2), 1920; Giannelli (1), 1922; Bonfiglio (1), 1922; Insabato (1), 1922; Mariconda (2), 1923; Guccione (1), 1929; Bignami (1), 1931; Camargo Barros (1), 1932; King—Meehan (1), 1936; Fittipaldi (2), 1937; Fontana (5), 1941; Bohrod (1), 1942; Nielsen—Courville (1), 1943; Merritt—Weisman (2), 1945; Masignani (1), 1948; McLardy (1), 1951; Garde—Girard—Palasse (1), 1952; Orlando (7), 1952; Roger—Poursines—Alliez (1), 1952; Seitelberger-Solms (1), 1952; Schwob *et al.* (1), 1953; Estrada—Fuste (1) 1952; Girard—Garde—Devic (2), 1953; Riese *et al.* (1), 1954; Jéquier—Wildi (2), 1955; Hagenau *et al.* (1), 1955; Seitelberger—Berner (1), 1955; Delay *et al.* (1), 1956; Boudin *et al.* (1), 1957; Tommasi (1), 1957; Gullotta—Mazzoleni (1), 1959.

D'Abundo's (1917) case was one of head injury with asymmetrical lesions in the corpus callosum. This together with that of Sarteschi (1911), Giannelli's third case (1931), and those of Charest (1945) and of Riggs and Boles (1945), have not been included because of insufficiency of the recorded facts.

The clinical symptoms and signs lack the extreme specificity of the pathological lesion, hence the condition is usually diagnosed post mortem. Marchiafava (1933) attempted to distinguish clinically between this rare syndrome (which he termed "dementia alcoholica progressiva") and the more usual form of alcoholic dementia viz. a chronic atrophy of the brain with arachnoidal thickening and occasional subdural hæmorrhages. There appears some justification for linking specific axial "necrosis" of the corpus callosum with a clinically terminal dementia in chronic alcoholics, characterized by the fairly sudden onset of convulsions and stupor, rigidity of the limbs, dyspraxia and dysphasia.

It seems to us however that in the Marchiafava-Bignami disease all of the cerebral symptoms cannot be accounted for by the callosal lesion alone, and that more widespread chemical or metabolic changes may possibly exist. The symptoms are compatible with widespread disturbances of brain-stem or cortical mechanisms and the severity of these symptoms and their fatal termination are difficult to relate in their entirety to the discrete focal lesions found after death.

XUM

INCIDENCE

Except in Italy the disease is rare in the experience of any pathologist. Apart from the early papers (Marchiafava and Bignami, 1903; Bignami and Nazari, 1915; Fontana, 1941) reports are usually of one or two personal cases. As a cause of dementia in chronic alcoholics this disease is far less common than degeneration of the cerebral cortex in chronic alcoholics or Korsakoff's psychosis with polyneuritis. In France it appears to be much less common than either cortical atrophy or Wernicke's disease, with the latter of which it may be associated. It seems unlikely that the rarity of Marchiafava-Bignami disease can be accounted for by the readiness with which the naked-eye appearance might be missed at post-mortem.

Nationality.—The early cases were all reported from Italy—Rome, Florence, Pisa, Parma. The notable exception was a paper by Laignel-Lavastine, who in 1920 reported 2 cases, one in a Frenchman and the other in a man who may have been of Alsatian extraction. During the past twenty-seven years, following Marchiafava's communication in London, cases have been described in French, Swiss, Spanish, Argentine, Cuban, Austrian, North American (U.S.A.), Hungarian and English natives.

The high incidence in Latins, especially Italians (*see* Table I) is remarkable. Barucci (1956) claims to have found the lesion in 2·4 per cent of 162 post-mortems on chronic alcoholics in Northern Italy. The opinion as to its more frequent occurrence in Italian nationals is supported by Agostini (1959) and by Bini (1959). Instances of the disease in expatriate Italians have been recorded by King and Meehan (1936), Merritt and Weisman (1945), Garde, Girard and Palasse (1952), and Hagenau, Bertrand, Christophe, and Godet-Guillain (1955). In the first of these no alcoholic history was ascertained but the others were all wine drinkers, as was Bohrod's case (1942), an expatriate Swiss possibly with some Italian blood. Gruner (1959) is of the opinion that the disease is not uncommon in Frenchmen but that it is seldom reported. The notion that the disease is indigenous to the Italian native can now no longer be sustained (*see* Table I).

Age.—The oldest patient recorded was 82 years (Guccione 1929 cited by Fittipaldi) the youngest 26 years (Estrada and Fuste 1952). The majority of cases occur between the ages of 40 and 60 years.

Sex.—The disease was thought at one time to affect males exclusively. However, Schwob *et al.* (1953) published one well-documented female case, and Delay *et al.* (1956) another: both showed other changes in the brain characteristic of alcoholism.

Since all the cases (so far as we know) have been diagnosed on the post-mortem findings, authors have had to supplement and reconstruct the

XUM

TABLE I.—NATIONALITY OF 88 RECORDED CASES

Italians 60	Living in Italy	56	Various Italian papers (1903–1937) cited by Fittipaldi (1937) Masignani (1948), Gullotta and Mazzoleni (1959)
	Living abroad ..	4	King and Meehan (1936), Merritt and Weisman (1945), Garde *et al.* (1952), Hagenau *et al.* (1955).
Non-Italians 28	French	10	Laignel-Lavastine (1920), Garde *et al.* (1952), Roger, Poursines, Allicz (1952), Schwob *et al.* (1953), Girard *et al.* (1953) (2 cases), Delay *et al.* (1956), Tommasi (1957), Boudin *et al.* (1957).
	Swiss	3	Bohrod (1942), Jéquier and Wildi 2 cases (1955).
	Spaniards	.. 3	Orlando (1952).
	Argentines	.. 3	Ibid. (1952).
	Albanian	.. 1	Ibid. (1952).
	Cuban ..	.. 1	Estrada and Fuste (1952)
	English ..	.. 2	McLardy (1951), Present case (1960).
	U.S.A. ..	.. 2	Nielson and Courville (1943), Riese *et al.* (1954).
	Hungarian (in Brazil)	.. 1	Camargo Barros (1932).
	Austrians..	.. 2	Seitelberger and Solms (1952), Seitelberger and Berner (1955).

clinical history by questioning the relatives and associates of the deceased. In the records available the history of alcoholism goes back for many years in almost all cases, but previous episodes of delirium tremens and of alcoholic psychoses are rarely mentioned. A history of malnutrition is more difficult to establish.

SYMPTOMS AND SIGNS

Mode of onset.—This is frequently sudden: the patient falls down and cannot get up, or lapses into a stupor, or is found unconscious. A bad bout of drinking without taking food, or an infection may precipitate the illness. On recovery from the initial symptoms the patient is often unable to speak. He appears to comprehend but is generally irresponsive. In conscious patients dysarthria and dysphasia are noted. References to dyspraxia are rare (3 cases only). Headaches and vomiting, or vomiting alone (perhaps due to œdema and brain-swelling), may raise the suspicion of cerebral neoplasm. There may be incontinence of urine or fæces. In rare cases the onset of the terminal illness has occurred while the patient has been under treatment in hospital and deprived of alcohol.

Psychical symptoms.—The patient is often admitted to a psychiatric clinic where he may be known because of previous admissions. In 12 cases the symptoms of onset were like those of delirium tremens, 6 cases showed agitation and 6 amnesic syndromes, whilst 8 patients had hallucina-

tions (visual or auditory). Dementia and stupor tend to supervene after a variable period of time.

Convulsions.—The rapid deterioration in the patient's mental state may be punctuated by convulsions sometimes focal, sometimes generalized.

Neurological signs.—Amongst the neurological findings most frequently noted are rigidity of all four limbs usually termed "generalized hypertonus." The posture may simulate that of decerebrate rigidity with flexion of the upper and extension of the lower limbs. In conscious patients a grasp reflex has been noted. If hemiplegia exists it is usually slight. Pyramidal signs on one or both sides are occasionally present. Tremulousness of the tongue and hands and clumsiness of arm movements are amongst other symptoms lacking specificity. An associated polyneuritis has been described in only 2 cases, those of Estrada and Fuste (1952) and Tommasi (1957).

Ocular signs.—The pupils may be unequal (McLardy, 1951; Orlando—Case 4—1952; Bohrod, 1942; Nielson and Courville, 1943) even in the absence of associated Wernicke's encephalopathy. Four patients showed abolition of the pupillary light reflex. Out of 36 well documented cases 8 showed optic atrophy or had post-mortem changes in the optic nerves or chiasma.

The *spinal fluid* when it has been examined has always been normal, both manometrically and on analysis. The EEG carried out on our patient and on others e.g. (Garde *et al.*, 1952) showed no focal lesion. Air encephalograms undertaken to exclude frontal tumour have been normal.

General state.—Malnutrition is not infrequently recorded and many patients showed atheroma. A few have had perforating ulcers on the soles of the feet.

Course and Prognosis

Duration of illness.—The illness appears to be a terminal one after years of heavy drinking, its duration varying from several months to a few days with an average of three to six weeks. It is of course difficult to say when a chronic alcoholic begins to develop symptoms for it may well be whilst he is still at work. There is slow decay of intellect and personality, with impairment of moral and social sense. The patient in the end, abandoned by his relatives and friends, often leads a solitary existence so that the commencement of his terminal illness cannot be determined with accuracy. The varying pathological features which have been described, such as presence or absence of œdema, glial reaction, vascular proliferation etc., appear to us to reflect the varying intensity and duration of the clinical illness.

Cause of death.—Death results in most instances from cardio-respiratory paralysis.

XUM

Relationship to Alcoholism

This association is most definite, and almost constant. Wine drinking to great excess is the usual story, but in our case and those of Seitelberger and Solms (1952) Seitelberger and Berner (1955) and McLardy (1951) the patient was credited with drinking beer and spirits. Garde, Girard and Palasse (1952) record the case of an Italian living in France who drank anise spirit and was grossly undernourished. The alcoholic drinks to which these patients with Marchiafava-Bignami's disease have been most commonly addicted are red wine (including "dago red"), rum, anise, schnapps, aquavit, whisky. Although in Europe the cases have been reported in areas where wine production or wine consumption is high, one is nevertheless forced to conclude that addiction to cheap red wine is not the essential nor the sole factor in ætiology. Indeed King and Meehan (1936) record an Italian male, 54 years old, thought to have a psychosis in whom no history of alcoholism could be obtained. The brain of this man showed degeneration of the middle zone of the corpus callosum, of the anterior commissure and of the optic chiasma. Merritt and Weisman's (1945) case, a male aged 56, was a psychotic who lived alone and was believed not to be alcoholic. Often it is difficult to separate malnutrition from chronic alcoholism. Not all the patients are of the peasant or labouring class though this is predominantly so.

Associated Diseases

Patients with this disease have sometimes been found to have aortic disease, auricular fibrillation or atherosclerosis, diabetes, and hepatic or pancreatic cirrhosis. Carcinoma of the tongue (Bignami and Nazari, 1915), and rectum (Riese *et al.*, 1954) may coexist with the alcoholism, and in these cases malnutrition may be an additional ætiological factor: likewise in the cases of the disease described in association with gastrectomy (Orlando, 1952). Hagenau *et al.* (1955) described an instance of the disease where carbon monoxide intoxication complicated the picture of alcoholism. Marchiafava (1933) recorded the case of an alcoholic who was asphyxiated by a bolus of food wedged in the pharynx.

Ætiology

The apparent liability of Latin races to this disease, yet its comparative rarity even in them makes it clear that some further factor or factors other than alcoholism must also be involved.

As the disease is commonest in those addicted to crude red wine it has been suggested that the responsible agent is some impurity in the beverage or an adulterating substance such as hæmatoxylin. In the present instance however, the patient's fancy latterly was almost entirely stout and beer, assimilated in the public houses of London. Such drinks are unlikely to have been contaminated and there is nothing to suggest

that he drank commercial methylated spirits (which contains pyridine and methyl alcohol) nor any other unusual form of "lacing." There is therefore no evidence in this case to suggest a contaminating injurious substance and in particular no reason to think that methyl alcohol was involved.

That the myelinolysis results from the avitaminosis to which alcoholics, on account of the chronic gastritis and its attendant anorexia, are often prone, is another possibility which has often been advanced. Gullotta and Mazzoleni (1959) favour the view that it is thiamine deficiency which gives rise to an alteration in the walls of the vessels of the corpus callosum. However, degeneration of the corpus callosum is not a recognized accompaniment of malnutrition *per se* with or without thiamine deficiency and conversely the Marchiafava-Bignami disease is only rarely accompanied by Wernicke's encephalopathy, or pellagra, and hardly at all by polyneuritis. This man's diet, however, was clearly inadequate and at necropsy he was greatly undernourished. Thiamine, it will be recalled, was given without apparent response but it was only during the last week of life.

It seems certain that there are marked racial differences in the incidence of the disease because it has been most commonly described in Italians and in those of other Latin races. It is clearly very rare in the United Kingdom and in the United States, while it has not yet been reported from Sweden where the average alcohol consumption is stated to be high and where, incidentally, the state of nutrition, and in particular protein consumption is high. The disease is unknown in Japan (Shiraki,1960).

Whatever the primary cause, the lesion is a demyelination continuing to complete necrosis of the central portion of the corpus callosum with or without similar degeneration of the white matter elsewhere, especially in the anterior commissure, optic chiasm, white matter of the cerebral hemispheres and cerebellar peduncles. With the demyelination there is a variable amount of axonal degeneration presumed to be secondary to this, but there is no gliosis. The absence of gliosis may be no more than an expression of the tempo of the disease although in multiple sclerosis the ultimate degree of gliosis is so marked as to be unique in neuropathology and as to suggest the presence of a fibre-stimulating factor. Demyelination, according to Hurst (1952), is to be regarded as the response of the white matter to a variety of noxious stimuli, of which cyanide provides the closest analogy to the disease under consideration. Ferraro (1933) for instance, by means of sodium cyanide was able to produce a massive demyelination of the white matter, the areas involved including the corpus callosum and anterior commissures. Hurst (1944) has commented on their resemblance to the lesions in Marchiafava-Bignami's disease. The experiments of Meyer (1932) with chronic cyanide intoxication in dogs, rabbits and guinea-pigs, those of Hurst (1940) on monkeys, and those of Lumsden (1950) on rats, all suggest that the central fibres of the corpus callosum are inherently vulnerable to this particular poison. Lumsden

XUM

for instance produced a lesion in 16 out of 37 rats which had survived thirty days of the regime. It is generally held that cyanide intoxication shows itself as an interference with the cytochrome oxidase system and Lumsden has suggested that it may be especially involved in the mitochondria of the oligodendrocytes. Experimental cyanide intoxication certainly provides the nearest approach we have to the Marchiafava-Bignami disease. The production of axial degeneration of the corpus callosum by feeding alcohol to dogs was reported by Testa (1929) but no one has so far succeeded in confirming his findings.

Some authorities, e.g. Orlando (1952), considers that Marchiafava-Bignami disease is a systemic affection of the commissures. To us this seems unlikely if only because the fibres are affected for only a portion of their length, and not (usually) out into the hemispheres; nor is there any reason to consider the commissural fibres as a "system."

The punched out lesion is more like an ischæmic softening than any other pathological condition; King and Meehan make this point strongly and we concur, our material being very similar to theirs. On the other hand, it was with some justification that Carducci rejected the designation necrosis. The point that he makes, namely, that the disease is essentially one of demylination with relative preservation of the axis cylinders is substantiated in the present case.

King and Meehan (1936) concluded that there was a likeness to multiple sclerosis; but with this we would not agree. It seems to us that the sharp demarcation affecting only a certain length of fibres whose cells lie in both hemispheres and with preservation of the peripheral (upper and lower) fibres on both sides strongly suggests that the anatomical basis of the lesion is one of ischæmia. The anterior cerebral arteries however, were patent throughout; indeed had they not been so the upper and lower layers would presumably not have been spared. No thromboses were seen in the capillaries of the damaged area and there was no endothelial proliferation. Little work has been done on the blood supply of the corpus callosum but if it is supplied and drained by penetrating vessels from the upper and lower surface then the middle layer forms a watershed area which may make it liable to ischæmia in particular conditions and especially in hypotensive phases. Feld and Gruner (1957) have reported the case of a 40-year-old male with multiple developmental anomalies of the brain including dilation of the left ventricle, septal agenesis, calcification of the choroid plexus and axial necrosis of the corpus callosum. His social history had not been abnormal. The softening of the corpus callosum was believed to have had a vascular origin consequent upon the malformation.

While the central white matter is susceptible to demyelination in anoxic states, the corpus callosum tends not to be involved. Hypoxia, therefore, as such cannot be advanced as a cause of the necrosis and this is confirmed by the absence of reported involvement of Sommer's sector or other areas

of the brain known to be sensitive to oxygen lack (Jéquier and Wildi, 1955). Neither do we find histological support for a view which has been advanced that axial necrosis of the corpus callosum may be the result of œdema: we would have expected more widespread changes in the white matter and especially a diffuse pallor and gliosis of the centrum semi-ovale.

Hypotheses advanced to date are little more than speculative and none save the possibility of certain people having some metabolic difference accounts for the rarity of the condition. It is possible that in these patients the medullated fibres, or more likely their ministering oligodendrocytes, are unusually susceptible to damage, and this may be bound up in some way with the allegedly relatively late myelinogenesis of the centrally placed fibres. It appears in fact that there is an individual, if not also a racial, susceptibility to central demyelination of the corpus callosum.

SUMMARY

A second case in an Englishman is reported of Marchiafava-Bignami's disease. He had been a heavy drinker of beer and stout. The clinical course consisted of a temporary bout of dysphasia followed four days later by an acute onset of aphasia with a period of unconsciousness and later convulsions. The illness lasted in all three weeks.

Post-mortem examination revealed pulmonary tuberculosis and evidence of general malnutrition. Demyelination was confined to the corpus callosum except for a few outlying patches which reached almost to the posterior horns of the ventricles. There was a diffuse loss of cells in the cerebral cortex and a reactive gliosis. There was no evidence of Wernicke's encephalopathy or of degeneration of the vermis of the cerebellum.

Current theories of ætiology are considered. It appears that there is an individual and to some extent a racial susceptibility to central demyelination of the corpus callosum.

Acknowledgments.—We are grateful to Professor Mario Gozzano for making available to us a copy of Dr. Carducci's original case report, and to Mr. Gordon Cox and Miss Margaret Doe for technical assistance. The case was originally admitted to the Paddington General Hospital under the care of Dr. R. D. Green.

REFERENCES

ADAMS, R. D., VICTOR, M., and MANCALL, E. L. (1959) *A.M.A. Arch. Neurol. Psychiat.*, **81**, 154.

AGOSTINI, L. (1959) Personal communication.

AKELEITIS, A. J. (1942) *Amer. J. Psychiat.*, **98**, 409.

—— (1944) *J. Neurosurg.*, **1**, 94.

ALPERS, B. J. (1936) *J. nerv. ment. Dis.*, **84**, 621.

ARIENS KAPPERS, C. U. and STRASBURGER, E. H. (1947) Anatomie Comparée du Système Nerveaux, Paris.

BAILEY, P., and BONIN, G. VON (1951) The Isocortex of Man. Urbana, Ill.

XUM

BARUCCI, M. (1956) *Riv. Pat. nerv. ment.*, **77**, 605.
BEEVOR, C. (1907) *Brain*, **30**, 403.
BIGNAMI, A. (1907) Policlinico (*Sey. prat.*), **14**, 460.
——, and NAZARI, A. (1915) *Riv. sper. Freniat.*, **41**, 81.
BIGNAMI, F. (1931–32) *Boll. Acad. lancis. Roma*, **5**, 128–133.
BINI, L. (1959) Personal communication.
BOHROD, M. G. (1942) *Arch. Neurol. Psychiat., Chicago*, **47**, 465.
BONFIGLIO, F. (1922) *Rivista sperimentale di Freniatria., Reggio-Emilio*, **14**, 219–250.
BOUDIN, G., BARBIZET, J., and BRION, S. (1957) *Rev. neurol.*, **97**, 433.
BREMER, F. (1952) *Rev. neurol.*, **87**, 65.
—— (1953) *J. Physiol. Path. gén*, **45**, 52.
——, BRIHAYE, J., and ANDRE-BALISAUX, G. (1956) *Schweiz. Arch. Neurol. Psychiat.*, **78**, 31.
——, and STOUPEL, N. (1956) *J. Physiol. Path. gén.*, **48**, 411.
——, and TERZUOLO, C. (1955) *J. Physiol. Path. gén.*, **47**, 105.
CAMARGO BARROS, J. DE (1931–32) *Trabalhos do Departamento de Anat. pat. Fac. Med., Sao Paulo*, **6**, 7.
CARDUCCI, A. (1898) Riv. di Psicol. Psich. e Neuropat. Fasc. 8–9, **2**. Rome.
CHANG, H.–T. (1953*a*) *J. Neurophysiol.*, **16**, 117.
—— (1953*b*) *J. Neurophysiol.*, **16**, 133.
CHAREST, F. (1945) *Journal de l'Hôtel Dieu de Montréal*, **14**, 390–393.
CLARK, W. E., LE GROS (1958) *In* Textbook of Human Anatomy. Edited by W. J. Hamilton. London. p. 803. Contribution starts on p. 687.
CURTIS, H. J. (1940*a*) *J. Neurophysiol.*, **3**, 414.
—— (1940*b*) *J. Neurophysiol.*, **3**, 407.
D'ABUNDO, G. (1917) *Riv. ital. Neuropat.*, **10**, 233.
DE ALBERTIS, D. (1920) *Riv. ital. Neuropat.*, **13**, 69.
DELAY, J., BOUDIN, G., BRION, S., and BARBIZET, J. (1956) *Rev. neurol.*, **94**, 596.
DEMEL, A. C. (1912) *Atti della Reale Accad. delle Scienze, Torino*, **47**,
EDINGER, L. (1911) 8th edition. Bau der nervösen Zentralogane des Menschen und der Thiere, Leipzig, **1**.
ESTRADA, R., and FUSTE, F. (1952) *Arch. Hosp. univ., Habana*, **4**, 371.
FELD, M., and GRUNER, J. (1957) *Pr. méd.*, **65**, 329.
FERRARO, A. (1933) *Psychiat. Quart.*, **7**, 267.
FITTIPALDI, C. (1937) *Riv. Pat. nerv. ment.*, **50**, 427.
FONTANA, M. (1941) *Osped. psichiat.*, **9**, 151.
GARDE, A., GIRARD, P. F., and PALASSE, A. (1952) *Rev. lyon. Méd.*, **1**, 99.
GIANNELLI, A. (1931) *Atti della Reale Accad. Med. di Roma*, **57**, 410. (Giving earlier references 1912, 1922).
GUIZZETTI, F., and TOMASINELLI, G. (1915) *Riforma Medica, Napoli*, **31**, 17, 449–454.
GIRARD, P. F., GARDE, A., and DEVIC, M. (1953) *Rev. neurol.*, **88**, 236.
GOLDSTEIN, M. (1914) *Z. ges. Neurol. Psychiat.*, **26**, 361.
GRUNER, J. E. (1956) *Rev. neurol.*, **94**, 682.
—— (1959) Personal communication.
GUCCIONE, F. (1929) *Riv. Pat. nerv. ment.*, **34**, 722.
GULLOTTA, F., and MAZZOLENI, G. (1959) *Arch. ital. Pat. Clin. Tum.*, **3**, 1494.
HAGENAU, J., BERTRAND, I., CHRISTOPHE, J., and GODET-GUILLAIN, G. (1955) *Rev. neurol.*, **93**, 656.
HURST, E. W. (1940) *Aust. J. exp. Biol. med. Sci.*, **20**, 297.
—— (1944) *Brain*, **67**, 103.
—— (1952) *Amer. J. Med.*, **12**, 547.
HYMAN, L. H. (1942) Comparative Vertebrate Anatomy, 2nd edition, Chicago. p. 436.
INSABATO, L. (1922) L'alcoolismo cronico. Soc. Edit. Lib., Milan.

IRONSIDE, R., and GUTTMACHER, M. (1929) *Brain*, **52,** 442.
JÉQUIER, M., and WILDI, E. (1955) *Schweiz. Arch. Neurol. Psychiat.*, **75,** 77.
——, —— (1956) *Schweiz. Arch. Neurol. Psychiat.*, **77,** 393.
KING, L. S., and MEEHAN, M. C. (1936) *Arch. Neurol. Psychiat., Chicago*, **36,** 547.
LANGWORTHY, O. R. (1932) *Arch. Neurol. Psychiat., Chicago*, **28,** 1365.
LAIGNEL-LAVASTINE, P. M. (1920) *Bull. Soc. méd. Hôp. Paris*, **44,** 1432.
LIEPMANN, H. (1905) *Münch. med. Wschr.*, **52,** 2322 and 2375.
——, and MAAS, O. (1907) *J. Psychol. Neurol., Lpz.*, **10,** 214.
LUMSDEN, C. E. (1950) *J. Neurol. Psychiat.*, **13,** 1.
MCLARDY, T. (1951) *Proc. R. Soc. Med.*, **44,** 685.
MARCHIAFAVA, E. (1913) *Riv. osped.*, **4,** 2.
—— (1915) *Quaderni di psichiat, Genoa*, **2,** 97–110.
—— (1933) *Proc. R. Soc. Med.*, **26,** (2), 1151–8.
——, and BIGNAMI, A. (1903) *Riv. Pat. nerv. ment.*, **8,** 544.
——, ——, and NAZARI, A. (1911) *Monatsschrift fur Psychiatrie and Neurologie*, **29,** 181–215 and 315–334.
MARICONDA, P. (1923) *Policlinico* (*Sey. prat.*), **30,** 860.
MASIGNANI, V. (1948) *Rass. Studi. psichiat.*, **37,** 93. Fasc. 1.
MERRITT, H. H., and WEISMAN, A. D. (1945) *J. Neuropath.*, **4,** 155.
MEYER, A. (1932) *Nervenarzt*, **5,** 229.
MILANI, A. (1914) Patologia del corpo calloso, *Thèse de Médecine*. Edition Giannandrea, Rome.
MINGAZZINI, G. (1922) Der Balken. Berlin.
NIELSEN, J. M., and COURVILLE, C. B. (1943) *Bull. Los Angeles neurol. Soc.*, **8,** 81.
ORLANDO, J. C. (1952) *Neuropsiquiatria*, **3,** 97.
RAMÓN Y CAJAL, S. (1911) Histologie du Système Nerveux de l'homme et des Vertébrés. Tome 11. Paris.
RAYMOND, F., LAJONNE, P., and LHERMITTE, J. (1906) *Encéphale*, 533.
RIESE, W., JONES, G. L., BEAMER-MAXWELL, E., and DAVIS, H. E. (1954) *J. Neuropath.*, **13,** 501.
RIGGS, H. E., and BOLES, R. S. (1944–45) *Quarterly Journal of Studies on Alcohol*, **5,** 361–370.
ROGER, H., POURSINES, Y., and ALLIEZ, J. (1952) *Rev. Neurol.*, **86,** 268.
ROSSI, O. (1910) *Rivista di Patologia nervosa e mentale.*, **15,** No. 6, 346–366.
SARTESCHI, U. (1911) *Rifista sperimentale di Freniatria*, **37,** 115–135.
SCHWOB, R. A., GRUNER, J., FOURCQUIER, E., HARL, J. M., FRANCON, J., and GUERRE, J. (1953) *Rev. neurol.*, **88,** 174.
SEITELBERGER, F., and BERNER, P. (1955) *Virchows Arch.*, **326,** 257.
——, and SOLMS, W. (1952) *Wien. Z. Nervenheilk.*, **5,** 354.
SHERRINGTON, C. S. (1889) *J. Physiol.*, **10,** 429.
SHIRAKI, H. (1960) Personal communication.
SMITH, K. U., and AKELEITIS, A. J. (1942) *Arch. Neurol. Psychiat., Chicago*, **47,** 519.
SPERRY, R. W. (1958) *In* Biological and Biochemical Bases of Behaviour, Edited by H. F. Harlow, and C. N. Woolsey, Wisconsin.
SUNDERLAND, S. (1940) *J. Neurol. Psychiat.*, **3,** 9.
TESTA, U. (1929) *Riv. sper. Freniat.*, **52,** 559.
TOMASCH, J. (1954) *Anat. Rec.*, **119,** 119.
TOMMASI, M. (1957) *J. Méd. Lyon*, **38,** 289.
WALBERG, F., and BRODAL, A. (1953) *Brain*, **76,** 491.

XUM

LEGENDS FOR PLATES

PLATE XXV

FIG. 1.—Coronal section of brain at the level of the anterior commissure. Note the central softening of the corpus callosum sandwiched between the upper and lower zones of well-preserved fibres. At this level the softening is rather more on the left than the right.

FIG. 2.—Coronal section of left hemisphere at the level of the corpora mammillaria. Celloidin section: Heidenhain's stain for myelin. ×0·75.

FIG. 3.—Coronal section through anterior part of splenium showing outlying areas of softening in the radiation of the corpus callosum. Celloidin: Heidenhain's stain for myelin. ×1·5.

PLATE XXVI

FIG. 4.—Upper edge of softened area in corpus callosum showing compound granular corpuscles (fat-laden macrophages) and a few surviving myelin sheaths. Note the abrupt edge to the main mass of myelin sheaths. Celloidin: Mallory's phosphotungstic acid hæmatoxylin. ×78.

FIG. 5.—Corpus callosum showing in softened areas normal-looking capillaries with compound granular corpuscles on the adventitia. Paraffin: Hæmatoxylin and eosin. ×78.

FIG. 6.—Section through centre of callosal softening showing relative preservation of a few islets of myelin. Celloidin: Heidenhain's method for myelin. ×90.

FIG. 7.—Corpus callosum showing the relative scarcity of axons in the softened (lower) area in contrast with the area of myelin preservation (upper). Note fragmentation and focal swellings on axons more especially at the edge of the lesion. Paraffin: Glees' stain for axons. ×90.

FIG. 1.

FIG. 2.

FIG. 3.

To illustrate article by R. Ironside, Francis D. Bosanquet and W. H. McMenemey.

XUM

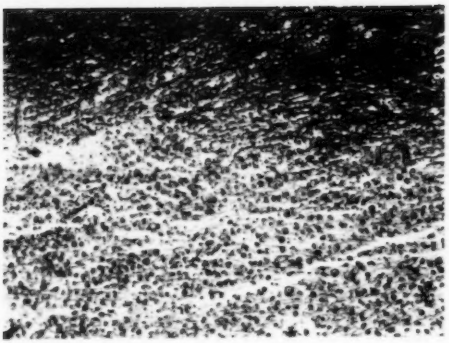


FIG. 4.

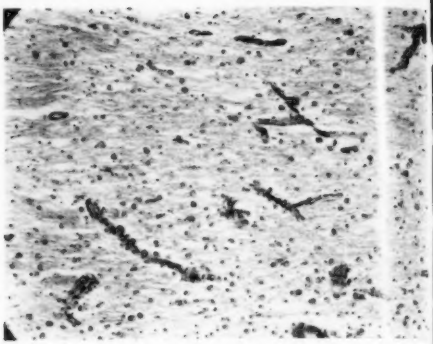


FIG. 5.

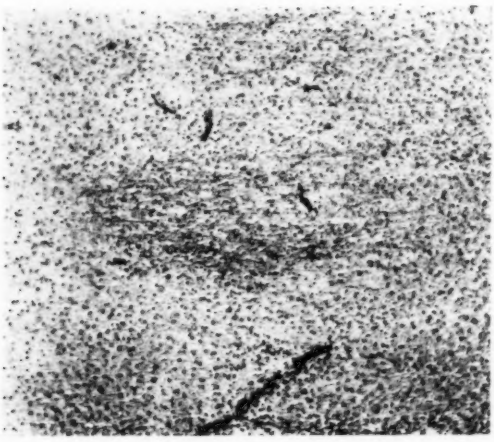


FIG. 6.

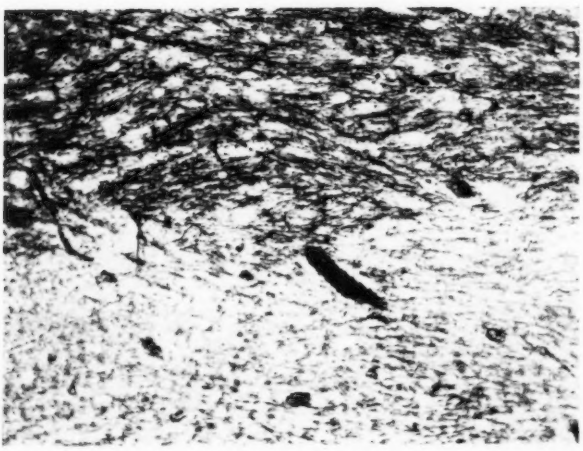


FIG. 7.

To illustrate article by R. Ironside, Francis D. Bosanquet and W. H. McMenemey.

CONGENITAL DYSLEXIA AND ASYMMETRY OF CEREBRAL FUNCTION

BY

WILLIAM GOODDY AND MARGARET REINHOLD

(*From The National Hospital, Queen Square, London, W.C.*1)

INTRODUCTION

DISORDERS of reading and spelling in otherwise healthy and intelligent children have been the subject of very many contributions to the literature of neurology and psychiatry in the past sixty years. As Riese (1954) has pointed out, Lordet described his own inability to read in 1843. We do not intend to discuss widely the literature on the subject, as Drew (1956) has provided an admirably complete review; Drew's paper contains 102 references.

There is still no general agreement about the most suitable name for the condition under discussion. The term "congenital dyslexia" is one of the least confusing or objectionable. Drew has pointed out that at least a dozen different names have been used in the past thirty years.

Cases of reading and writing difficulties are well known to neurologists and psychiatrists, but they are regarded as very uncommon in Great Britain. In Denmark, however, the condition is considered to be quite common and one estimate suggests that 10 per cent of the population of Denmark may be affected, (Hallgren, 1950). We believe that the condition is more common in Great Britain than is at present supposed. We have been able to collect more than 20 cases from routine neurological practice without advertisement of our interest in the subject.

Symptoms and signs of congenital dyslexia

The child suffering from congenital dyslexia may be regarded as normal during the early stages of education. Difficulties begin to be noticed with reading and writing, as a rule at about the age of 6 or 7 years, when the child falls behind the general level of the class. It may then be noticed that the patient has not properly mastered the alphabet, and that all words with which he is not extremely familiar cannot be recognized in reading, nor spelt in writing. The reading and spelling difficulties are closely linked. The child with congenital dyslexia is unable to translate the words he hears

into meaningful written symbols—hence his inability to spell. He is unable to translate the words he sees into meaningful spoken symbols—hence his inability to read. The child does, however, have a good grasp of spoken language and he often talks fluently, using a large vocabulary.

The problem varies in degree from a slight difficulty in spelling or reading to a severe disability, when the child may be unable to spell or read even two-letter words.

In addition to the reading and writing difficulty, there is invariably a right-left disorientation of some degree. Patients show confusion between right and left long after the age when children normally achieve a more or less automatic sense of knowledge of rightness and leftness. In a severe case, the child may be unable to distinguish which is his right and which his left side. A less severe disturbance may show itself as an inability to tell the time, because it is impossible for the child to say whether the hands of the clock point "to" the hour or "past" it. Difficulty may be experienced in tying shoe-laces or bows, or in opening doors which require right-to-left (or *vice versa*) directional movements. There is occasional difficulty also with "up and down" or "North" and "South" directions. In the mildest case of right-left disorientation, the disturbance may be elicited only by detailed testing. The right-left disorientation may be seen also in association with the spelling difficulty. Children tend to put letters in a wrong right-to-left order. For example, T C A for C A T; or T S E N or S T E N for S E N T.

The mirror-reversal of letters or numbers is also commonly seen. For example, "d" is written for "b", "q" for "p".

Patients commonly experience difficulty with other symbols, especially those of arithmetic and algebra. They may, however, have no particular problems with geometry. In arithmetic, the symbols of "+" and "×" are often confused.

Secondary emotional disturbances are common in the patients, since their problems are usually not understood by parents or teachers. Laziness or backwardness is often regarded as the cause of the educational difficulties. Unusual mood and behaviour in a child who is learning to read and write may indicate the presence of the congenital difficulty.

It must be emphasized that patients with this condition should be distinguished from those suffering from:

(i) general mental deficiency;
(ii) defective vision or hearing;
(iii) brain damage, such as may result from maturation defects, anoxia, injury or infection in early life;
(iv) primary emotional disturbances;
(v) lack of education.

The disability is sometimes familial (fig. 1).

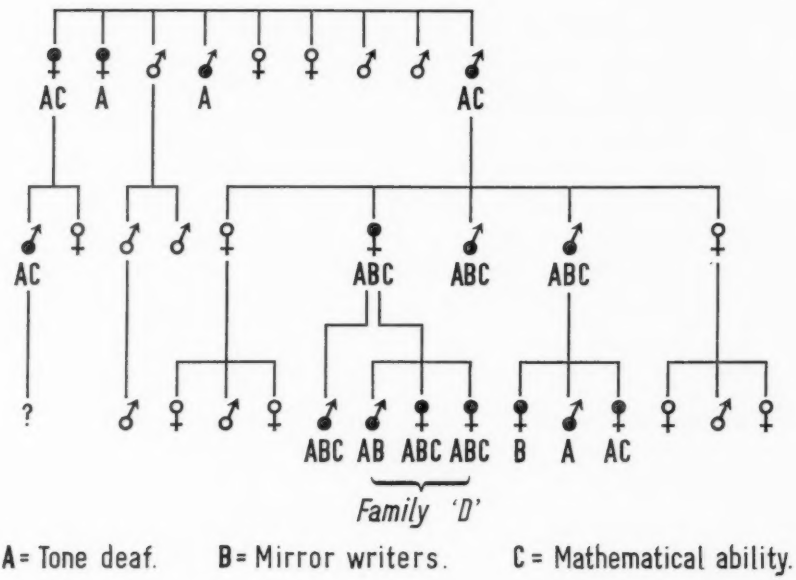


FIG. 1.

Illustrative Case History

L. H., aged 10 years: National Hospital No. 47785.—The patient was right-handed for batting, bowling and throwing. He used his left hand for writing.

Family History.—1 sister who was right-handed. His parents were right-handed.

Previous History.—The patient had a normal birth, sat up, walked and talked at the normal ages.

No previous illnesses of any importance. The patient was a bright intelligent child. No difficulties of any kind were noticed until he began to learn reading and spelling at achool.

The patient was referred to Dr. Gooddy at the age of 10 years with the following report from his tutor (Mr. H. P. Snowden, M.A.Oxon.):

> "I am of the opinion that there is some lack of co-ordination, and that what has been taken for laziness, is, in reality, inability on his part. It would also appear that there is some suppressed fear, of which he may not be aware, that he will not read a word right, so he makes what is often a wild guess.
>
> "I have noticed the following points:
>
> He reads very slowly, following the text with his finger.
>
> He sometimes reads quite a long word with little hesitation, e.g. IMMEDIATELY, but boggles over 3 and 4 letter words.
>
> He has difficulty over the letter "R" when not an initial letter.
>
> He frequently reverses letters, reading 'TORT' for 'TROT', and 'ON' for 'NO' and vice versa. He frequently reads 'THE' for 'AND,' both of which seem familiar combinations of letters. He has difficulty in distinguishing words beginning with 'W' and 'Y.'
>
> "The second reading of a passage is very little better than the first.

"The boy is well up to average intelligence, and is interested in most boyish hobbies, except that when reading is required, he will not attempt it. He is fond of being read to, where he does not have to make the effort himself."

The child was bright and intelligent during the many examinations and co-operated well at all times. He concentrated well and seldom complained, although he must often have found the examinations tedious and difficult.

Neurological examination.—Normal routine findings.

Speech.—Normal. Vocabulary: good. Asked to tell the story of William Tell, recently learned at school, he was able to do so with great accuracy.

Alphabet.—Recited correctly as far as O—left out P—went to Q. Told "R"—went on correctly but again became mixed up towards the end.

Writing (fig. 2) (i) his name
(ii) alphabet
(iii) numbers 1–10

Asked to recite the months of the year.—Began with February, January—April, March, June.

Started again: January, March—covered in confusion, could not go on.

Reading.—The patient could read the alphabet correctly and the separate letters. He was perfectly able to read many words with which he was very familiar—even complicated words, but certain simple words with which he was not familiar could not be read. For example, he could read "BRIGHT" but not "BRIGHTER". He could

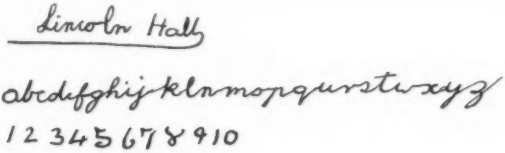


FIG. 2.

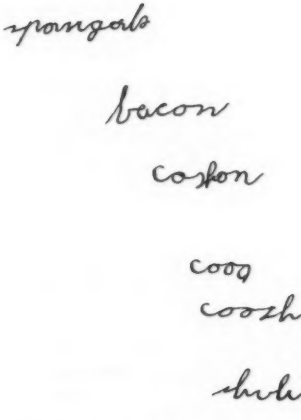


FIG. 3.

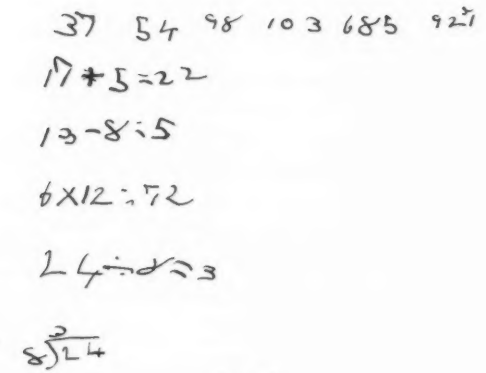


FIG. 4.

read "JEWEL", "BREAD", and "MASTER", but not "MIRACLE" or "GARLAND."

(In this condition, it is quite possible for a child to make mistakes with reading, writing, or reciting the alphabet, yet to be able to read fairly complicated words, as the latter are learned and memorized as visual patterns, not associated with sound or with the separate letters of the alphabet).

Spelling to dictation (fig. 3):

Sponge cake
Bacon
Cushion

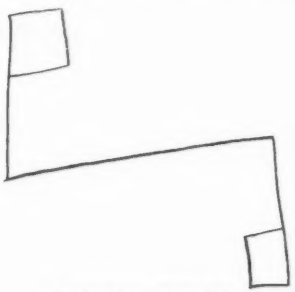
Arithmetic fig. 4: (Some slight temporary confusion regarding the signs × and +).

Drawing.—Patterns to copy from a given page: fig. 5. Patterns to copy from memory: fig. 6. (Note right-left disorientation).

Right-left orientation.—Confusion as demonstrated by the following tests:

(1) Asked to indicate right and left hands on figure drawn (fig. 7).

(2) Directions on map (fig. 8). The child was presented with a map of streets and blocks of houses. He was asked to imagine himself walking along the streets, and then, at certain corners, he was asked to take a turn to the right or the left. This test,



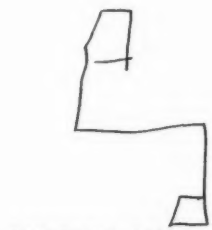
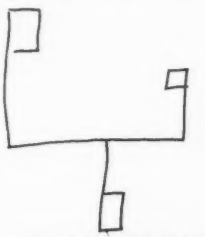


FIG. 5.



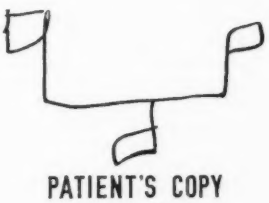


FIG. 6.

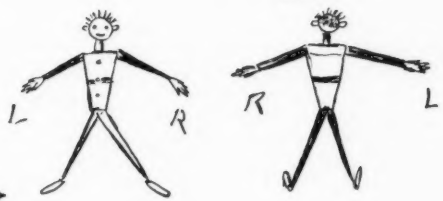


FIG. 7.→

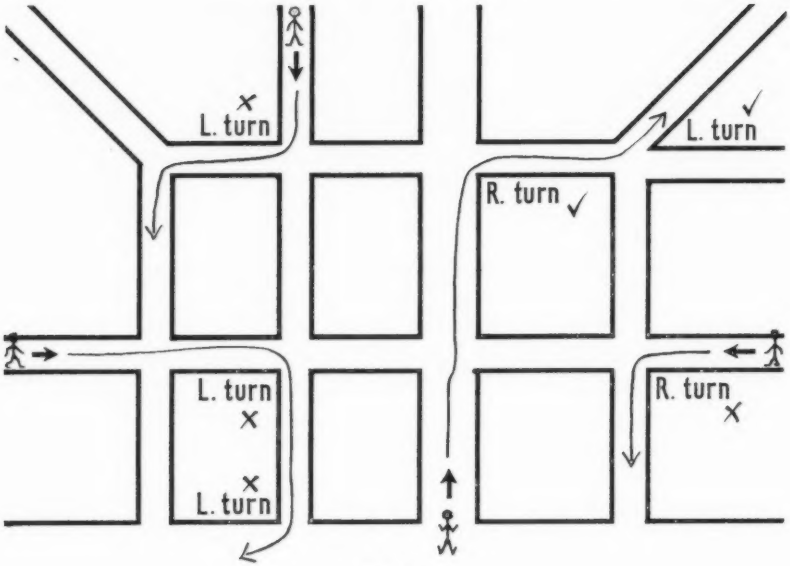


FIG. 8.

requiring the concept of the body in all degrees of positions around the central axis, may be used to demonstrate right-left confusion even when the confusion is slight.

Telling the time.—Some faults on account of right-left disorientation.

Koh's Blocks.—Constant reversal of patterns as shown (fig. 9). The following test was also performed. The child was asked to make words out of the following letters:

G O A L B E E T

He was quite unable to distinguish the two obvious words—GOAL and BEET, as he was unfamiliar with them. He wrote: BEE, BE, BOAT, REAL, REEL.

Results of training.—It was found that the patient could both read and write the word "SEARCH." He was asked to read this word several times: "RESEARCH." He was able to do so correctly. He was asked to look very carefully at the spelling. The word was then removed from his sight and he was asked to write it. He wrote as follows (fig. 10). He was then asked to write "SEARCH." He wrote the word correctly as shown (fig. 11). This word was covered and he was again asked to write "RESEARCH." He wrote the word as seen on fig. 12. It was pointed out the "E" was missing. Finally, he was able to write the word correctly.

Similar training was undertaken with the two words "GERANIUM" and "SWEATER." At the end of one lesson, after many mistakes, he was able to write these words correctly. (fig. 13).

At his next interview, a few days later, he spontaneously said he remembered the two words. He said them aloud, offered to write them, and wrote: (fig. 14).

Children with this congenital difficulty, however, can be taught by constant repetition to learn the spelling of words. Treatment will be discussed below.

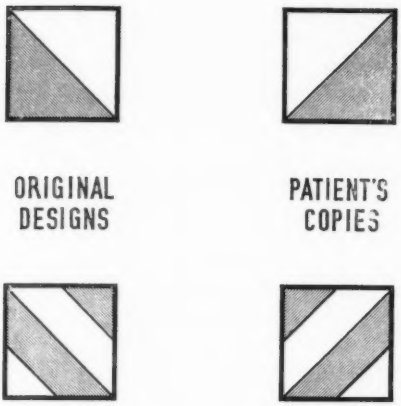


FIG. 9.

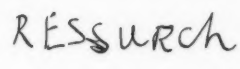


FIG. 10.

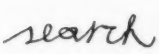


FIG. 11.

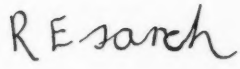


FIG. 12.

FIG. 13.

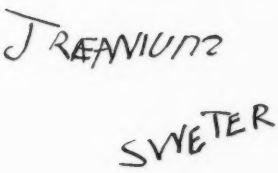


FIG. 14.

Other common findings are:
(1) Reversals of figures or letters, for example:—
or even complete mirror writing as:

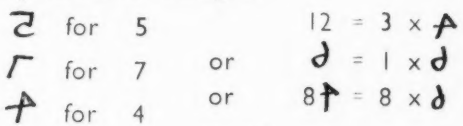


FIG. 15.

(2) The placing of letters which should come at the end or near the end of the word, at or near the beginning of the word, for example:

HRUT for HURT
EIDDE for EDDIE
and NONTOR for NORTON.

(3) In telling the time, complete right to left reversals and up and down reversals may occur, for example: fig. 16: Time described by a patient as ten to four; fig. 17: Time described by a patient as five to twelve.

Our patient, L. H., was tested in a great variety of other ways. For

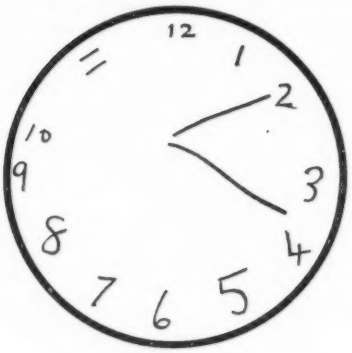


FIG. 16.

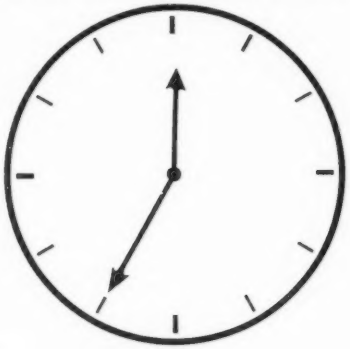


FIG. 17.

Munc upon a time there was a Woodcutter how was wrundring in the woods and sundele he

FIG. 18.

Smith

Smijth

FIG. 19.

Historical
Implications
various
busso
~~Co~~ Kudenser

FIG. 20.

English Christine Smith. 60ct.

A modern Myth.

The year 2,060 dawned over a dismal England. For the first time in a thousand years the iron heel of an invader was again grinding on her people. The monarchy had been overthrown also the Church and a new heathen goverment had been set up.

FIG. 21.

example, we did not find he could read or write mirror writing any better than normal writing. Teaching spelling by phonetic methods met with total failure. Categorizing particular sounds or words was equally unsuccessful in helping him to learn them, for example:

All meanings of the sound of "B"—Bee in hive, Be good, eating Beans;

All the meanings of the sound "TOO"—Two people, To the bath, He is too good.

The characteristic spontaneous spelling of one patient when writing a school essay is shown here:

(Once upon a time there was a Woodcutter who was wandering in the woods and suddenly he . . .) written as (fig. 18).

Discussion

We are normally able to convert with ease sounds which we perceive into meaningful symbols of a different sensory category. (Perception is defined as the qualitative experience of a conscious person, evoked by or accompanied by a series of events including the unconscious reception, selection, differentiation and integration of afferent stimuli: these stimuli are perceived as sensations which can be described in terms of symbols).

Sounds heard may therefore be expressed in terms of spoken words or of written symbols. Complex experiences of multiple sensory perceptions may be expressed in terms of paintings or sculptures; that is, in terms of spatial symbols and colours. (A blind man once said he imagined that the colour red was "like the sound of a trumpet"). Spatial sensory perceptions may be translated into spoken words, into two-dimensional constructions or into music symbols—musical notation, or music performed with instruments. In the same way, spoken words, two dimensional diagrams, three dimensional constructions, mathematical formulæ, music, may all be translated into perceptions of a spatial nature. Animals with powerful olfactory perceptions are able to estimate distance and direction and accurately to locate position by means of smells.

The ability to translate symbols of sensory perceptions of one sensory category into those of another category is accepted as a normal, automatic function. This ability must, however, require complicated cerebral and psychological processes; and it occurs mainly as the result of learning in childhood.

In congenital dyslexia, there may exist, among other abnormalities, a defect in the organization of spatial perception, resulting in the right-left confusion. The main symptoms of the condition are that the affected child cannot translate heard symbols into written symbols, nor written symbols into spoken symbols (equivalent to heard symbols).

The latter aspect of the difficulty is often less marked than that of translating sounds into meaningful writing.

XUM

It is well known that many children suffering from congenital dyslexia belong to a family where one parent or relative may be right-handed and another left-handed. Many children with the condition are themselves not strongly right or left-handed. Some patients are right-handed but left-footed, or vice versa, or they may be right-handed and left-eyed. The lack of a firmly established right or left-handendess may indicate the lack of one markedly dominant hemisphere of the brain. The lack of differentiation between the functions of one hemisphere and the other may be a causal factor of the condition. We wish to put forward the theory that *asymmetry* of right and left cerebral hemisphere functions is normally established as the child grows up; and that this asymmetry of function is closely related to the performance of reading and writing. We believe that children with congenital dyslexia fail to establish asymmetry of function in the cerebral hemispheres.

In his remarkable monograph "The Master Hand," Blau (1946) reviews widely the literature concerning the origin and development of handedness and its relation to language functions. As a result of this research, he states:

> " . . . The historical development and structure of language illustrate very clearly its close association to preferred laterality. Language is essentially a tool for communication which exploits the receptive capacities of sound production, gesturing and drawing. The intermediary agent for this communication is always some visual or auditory production. It is in the structure of those productions that the factor of lateralization is significant."

Blau goes to great lengths to illustrate that *handedness* in early man (as seen in the production of tools and implements meant for the use of one or other hand) and *writing* (of right-to-left or left-to-right directional flow) developed in association with one another.

It may be therefore, that the development of *asymmetrical* functions of the two hemispheres of the brain are linked to handedness, and the ability to write in a horizontal directional flow. That is to say, handedness and writing and reading ability are *all* equally the outcome of the gradual development of *asymmetrical* functions of the cerebral hemispheres, and are therefore closely functionally linked.

In a previous paper (Gooddy and Reinhold, 1954) we stated that the brain may be likened in certain of its functions to a calculating machine, although we were careful to point out that the human being is *not* a calculating machine. If the nervous system, and the brain in particular, functions in a way analogous to the calculating machine, it requires an input of information before it can become responsible for executive action or for abstractions from simple input information suitable for the derivation of judgments and temporally delayed efferent activity.

It is well-known in electronic engineering that "information" content is associated with asymmetry. This statement is easily understood from a simple example. The circle of a compass dial is divided into 360 separate degrees, each of which implies a certain degree of deviation from a particular axis (usually from the earth's magnetic pole's axis). Only when a particular point on the circumference of the circle is selected does a specific information idea come into force. The compass is thus a means of making use of a mono-directional system selected from the 360 available directions. The arrow point of the compass thus conveys the maximum degree of asymmetry. Similarly, in order to describe a spherical multicellular organism composed of smaller spherical cells, one needs the description only of the spherical components. By contrast, to reconstitute an asymmetrical body such as a stone, it is necessary to provide a description of all the components of the stone separately before a duplicate can be made.

We wish to relate these theoretical ideas to congenital dyslexia. We suggest that children with congenital dyslexia may be suffering from an abnormality of cerebral function which results in a deficiency of, or inability to co-ordinate, sensory information. The deficiency or lack of co-ordination of sensory information may cause an inability to translate heard symbols into meaningful written symbols (and vice versa) and right-left confusion.

The cerebral defect may be related to a too close similarity of function, that is, a lack of asymmetrical function of the two hemispheres.

Treatment

Treatment is at present very limited, but there are several obvious ways, derived from the theory outlined above, in which patients can be helped.

(*a*) An explanation of the problem to the child, and to his parents and teachers is of great value. The child at once responds with relief and renewed efforts as soon as he realizes that his mysterious and inexplicable difficulty has a rational explanation. He is encouraged to acquire minimum educational standards which will allow him to pass on to develop special talents of a non-literary kind. It is helpful to let the child see other children with the same complaint, and if possible to train several children together.

(*b*) Phonetic methods of teaching spelling and reading have to be abandoned. The child has to learn, as a feat of memory, every letter of the alphabet, so that no mistakes are ever made. Only then may he be given progressively larger collections of letters, forming simple and later complex words, each group being perfectly learned and retained over daily testing before new groups are allowed. As new groups of words are added the old ones must be kept in practice.

(*c*) Some trick for remembering right and left has to be devised. The method must use the asymmetry derived from a sign on one side of the

XUM

body which signifies the right. A mark on the hand, or a watch, or a piece of thread, or an object in the trouser pocket, may serve. The mark side is the right side. The left side is easily learnt, being the "other" side from the mark used to convey the information derived by selecting a feature denoting asymmetry.

(*d*) Writing in sand or with poster paints with large gestures may be helpful, as is the making of letters with clay or plasticene.

Progress is invariably slow in the early stages of treatment.

Prognosis

For some unknown reason, the condition of congenital dyslexia is at its worst in the earlier years of childhood (say from 6 to 12 years) and may improve of its own accord in the early "teens." (Fig. 19—writing aged 9 years; fig. 20—writing aged 15 years; fig. 21—writing aged 18 years). Some children with severe reading and spelling difficulty at the age of 7–9 years learn to read and write at a low average standard by the time they reach 15 years old, but the improvement does not necessarily take place. Certain individuals remain severely disabled all their lives. Some "illiterates," of which there are enough to cause national anxiety—a surprisingly large number were discovered among National Servicemen—may be suffering from congenital dyslexia.

Children with this disability, even of high intelligence, may never attain a standard of reading and writing commensurate with their intelligence. Most sufferers remain hampered by their disability all their lives. Careers which do not greatly depend upon reading and writing should therefore be chosen for them.

Summary

Congenital dyslexia is a condition which is possibly due to an inherited defect of function of the brain. The condition is not, as far as is known, due to an organic disturbance of brain tissue (that is, to failure of development, or tumour, or atrophy) or to metabolic disturbance in nervous tissue. It seems that certain specific cerebral activity is necessary to enable an individual to translate sound to writing and writing to sound. In the congenitally dyslexic individual, this specific cerebral activity may be defective in function. It is suggested that the condition may be the result of the lack of asymmetry of function of the cerebral hemispheres.

REFERENCES

Blau, A. (1946) "The Master Hand"; Research Monographs—No. 5, American Orthopsychiatric Association, New York.

Drew, A. L. (1956) *Brain*, **79**, 440.

Gooddy, W., and Reinhold, M. (1954) *Brain*, **77**, 416.

Hallgren, B. (1950) *Acta psychiat. Kbh.*, Suppl., 65.

Riese, W. (1954) *Bull Hist. Med.*, **28**, 237.

REDUCTION OF VOCABULARY IN APHASIA[1]

BY

HILDRED SCHUELL AND JAMES J. JENKINS

(From the Division of Neurology, University of Minnesota; The Neurology Service, Minneapolis VA Hospital; and the Department of Psychology, University of Minnesota)

IN the framework of present-day research it appears most meaningful to define aphasia as a reduction of language resulting from brain injury, which cuts across various language modalities, such as comprehension of spoken language, speech, reading and writing, and upon which specific perceptual, motor or sensorimotor deficits may or may not be superimposed.

Freud (1953) proposed regarding the speech area as a field, the peripheries of which were the primary motor and sensory areas. He suggested that if one imagined a movable lesion in this field, the closer the lesion approached one of the primary sensory or motor areas, the more observed symptoms could be expected to partake of the characteristics of the given area.

Penfield and Roberts (1959), from a ten-year study of language disturbances observed during seizures, sodium amytal injections, electrical stimulation of the cortex of conscious and co-operating patients, cortical excisions and other brain surgery, reached a similar conclusion. Roberts states that lesions in specific sites may result in specific clinical syndromes, although he points out that this does not mean that there is a centre in Broca's area for the motor patterns of words, or one in the angular gyrus for recognition of letters, numbers or words. He adds that there is not a single case in the literature of "visual-verbal agnosia," for example, without other defects or without ability to recognize some word at some time, if the examination is detailed enough. This conclusion is compatible with findings reported by Head (1926), Weisenburg and McBride (1935), Wepman (1958), and Schuell and Jenkins (1959).

In a preliminary report of a study still in progress consisting of a factor analysis of test responses of 168 aphasic patients in 19 hospitals, Wepman

[1]This investigation was supported in part by Public Health Service Grant B 1948, from the National Institutes of Health, Public Health Service.

XUM

and Jones (1958) have tentatively interpreted the major factor identified as "probably indicating a general ability of patients to manipulate verbal symbols." At the same time they found separate scores for visual and auditory stimuli, and oral and graphic responses extremely useful in characterizing individual patients. Both these findings are in essential agreement with the point of view expressed by Freud (1953), by Roberts (1959), and by Schuell and Jenkins (1959), that is, that there is a general language deficit in aphasia, but specific symptomatology differs from patient to patient. Both aspects of the clinical picture must be understood.

In a previous study by the present authors, responses of 123 aphasic patients to 18 language tests which sampled various stimulus and response modes and covered a wide range of difficulty, were found to be scalable by the Guttman technique (1947). This means briefly that if tests were ranked in order of difficulty defined by the number of patients who failed each one, and if patients were ranked in order of severity of aphasic involvement defined by the number of tests failed by each patient, it was possible to predict from one scale to the other with about 90 per cent accuracy. This is considered evidence of a single dimension of language deficit present in all these patients, at a statistically significant level, in spite of perceptual, motor and sensorimotor concomitants of brain damage present in some patients and not in others, and reflected in test responses. It means that nineteenth century theories of isolated disturbances of single language modalities resulting from circumscribed lesions of topographical cortical areas are no longer tenable, but neither are theories of cortical equipotentiality.

It is the purpose of this paper to explore one aspect of the general language reduction in aphasia, namely, reduction of vocabulary, and to present data showing some of the ways in which this reduction is manifested in various language modalities.

Reduction of Vocabulary in Comprehension of Spoken Language

It has been observed clinically that when aphasic patients were asked to point to objects or pictures named by the examiner, they tended to confuse (*a*) words which sound alike (goat, coat; lake, rake), an auditory perceptual confusion; (*b*) words associated in meaning or experience (sky, blue; chair, table), a semantic confusion; and that only a few patients, in general those most impaired, confused dissimilar unrelated words.

To explore these observations in a systematic manner, a test was constructed consisting of 15 picture cards. Each card contained four pictures: (*a*) the test object; (*b*) an object whose name rhymed with the test word; (*c*) an object closely associated with the test object, as

evidenced by the fact that it was a popular response to the test word on the Kent-Rosanoff Word Association Test (Kent and Rosanoff, 1910; Russell and Jenkins, 1954); and (*d*) an unrelated object. The following are examples of the pictures contained on the first three cards, with the test word first:

(1) *Chair*, stair, table, apple.
(2) *Bread*, bed, butter, boy.
(3) *Man*, pan, woman, star.

A card was presented to the patient; the examiner spoke the test word only; the patient was required to point to the object named. Two presentations were made of the set of pictures. On the first presentation the stimulus was the word spoken by the examiner. This will be referred to as the auditory presentation. On the second presentation, a printed word on an individual card was presented at the same time the word was spoken by the examiner. This will be referred to as the combined auditory and visual presentation.

The test was administered to an unselected sample of 117 aphasic patients seen on the Neurology Service at the Minneapolis VA Hospital between March 1957 and November 1959. All patients had been previously examined by means of the Minnesota Test for Differential Diagnosis of Aphasia (Schuell, 1955*a*) developed at this centre, and classified in clinical groups previously described by Schuell (1955*b*) on the basis of these findings. These classifications are briefly as follows:

Group 1.—Severe impairment, amounting to almost total loss of functional language skills in all modalities.

Group 2.—Reduction of vocabulary and retention span in all modalities.

Group 3.—Reduction of vocabulary and retention span in all modalities, with coexisting involvement of visual processes.

Group 4.—Reduction of vocabulary and retention span in all modalities with coexisting involvement of sensorimotor processes.

Group 5.—Simultaneous involvement of auditory, visual and motor processes with some functional language skills retained.

In addition 3 patients were classified as *Group* 6, a clinical syndrome characterized by auditory imperception with retention of some spontaneous speech. One of these patients was tested on two admissions, a year apart, making a total of four records for Group 6. This is the only such duplication in the series. 2 patients were unclassified because they were not considered physiologically stable when tested. These data are contaminated to some extent by inclusion of patients who had undergone intensive treatment for aphasia for varying periods of time, as well as patients who had received no treatment. 50 patients made no errors on either presentation, leaving data from 67 patients, of whom all made at least one error, to be analysed.

XUM

Findings

Table I shows the number, the mean number and the percentage of each type of error, and the total errors made by patients in each clinical group, and for the whole sample, for both the auditory and the combined presentations.

TABLE I.—NUMBER, MEAN AND PERCENTAGE OF ERROR TYPES AND TOTAL AUDITORY RECOGNITION ERRORS FOR CLINICAL GROUPS

	Group	*N*	*Stim.*	*Aud. errors*	*Ass. errors*	*Ran. errors*	*D. K.*	*Total errors*
N	1	15	Aud.	27	44	19	2	92
M				1·81	2·95	1·27	·13	6·16
%				29%	48%	21%	2%	100%
N			Comb.	23	40	17	4	84
M				1·54	2·68	1·14	·27	5·63
%				27%	48%	20%	5%	100%
N	2	6	Aud.	2	9	0	1	12
M				·33	1·50		·17	2·00
%				17%	75%		8%	100%
N			Comb.	1	4	0	0	5
M				·17	·67			·84
%				20%	80%			100%
N	3	7	Aud.	3	10	1	0	14
M				·43	1·43	·14		2·00
%				22%	71%	7%		100%
N			Comb.	0	10	0	0	10
M					1·43			1·43
%					100%			100%
N	4	4	Aud.	3	11	0	0	14
M				·75	2·75			3·50
%				21%	79%			100%
N			Comb.	2	6	0	0	8
M				·50	1·50			2·00
%				25%	75%			100%
N	5	29	Aud.	12	46	2	18	78
M				·41	1·59	·07	·62	2·69
%				15%	59%	3%	23%	100%
N			Comb.	8	40	1	4	53
M				·28	1·38	·03	·13	1·83
%				15%	75%	2%	8%	100%

Continued on next page

N	6	4	Aud.	1	9	0	1	11
M				·25	2·25		·25	2·75
%				9%	82%		9%	100%
N			Comb.	1	3	0	1	5
M				·25	·75		·25	1·25
%				20%	60%		20%	100%
N	Unclass.	2	Aud.	0	5	0	0	5
M								
%								
N			Comb.	0	2	0	0	2
M								
%								
N	Total	67	Aud.	48	134	22	22	226
M				·72	2·00	·33	·33	3·37
%				21%	59%	10%	10%	100%
N			Comb.	35	105	18	9	167
M				·52	1·57	·27	·13	2·49
%				21%	63%	11%	5%	100%

Several findings are of interest here. The first is the relatively high frequency of association errors. When the auditory stimulus alone was presented, 59 per cent of all errors were association errors, that is, confusion of words like chair and table, man and woman, house and car, nose and mouth and so on. 21 per cent of the total errors were confusions of words which sound alike, such as chair and stair, bed and bread, house and mouse, and nose and rose. 10 per cent were confusions of unrelated words such as chair and apple, bread and boy, man and star, and house and fish; 10 per cent were "don't know" responses. There were about six times as many association errors as random errors. 86 per cent of all the random errors were made by the 15 Group 1 patients, the most severe aphasics. Group 2 patients, who were in general the least impaired, made no random errors, and 75 per cent of their total errors were association errors. One random error was made in Group 3 and two in Group 5. Since patients in both of these groups have involvement of visual processes, it is possible that these minimal errors could have been related to the pictures rather than the words. For example, it is possible that a patient might fail to see the correct picture and respond by guessing.

When combined visual and auditory stimuli were presented, the task became easier for most patients. The mean number of total errors decreased for all clinical groups, and the mean number of each type of error decreased for the total sample. The decrease in total errors was

XUM

significant beyond the ·001 level of confidence and the decrease in association errors beyond the ·05 level. In other words, using combined visual and auditory stimuli helps most aphasic patients. The correlation between the scores of patients on the first and second presentations was +·84. This indicates that, in the main, the addition of the printed stimulus raised the frequency of correct identifications in a relatively uniform fashion. The subjects received about the same relative ranking on the two administrations. However, close examination of the data revealed that the combined stimuli were most helpful to patients in Groups 2, 4 and 6 who were presumably able to make the best use of added visual cues. Since the number of patients in some of the individual groups is too small for meaningful analysis, the percentage of error reduction with the combined stimuli is shown for patients in Groups 2, 4 and 6 combined, and compared with the reduction in Groups 1, 3 and 5. It is probable that in Group 1 the language reduction is so great that the printed word does not help much; in Group 3 and 5 impairment of visual discrimination and recognition cuts down the effectiveness of the visual cue, although it still provides some help. The presence of the visual stimulus appears chiefly to reduce the number of "don't know" responses. These data are shown in Table II, which simply indicates that all aphasic patients do not utilize visual cues equally, and that it is possible, on the basis of comprehensive clinical examinations to predict

TABLE II.—NUMBER, MEAN NUMBER AND PERCENTAGE OF ERROR REDUCTION ON AUDITORY RECOGNITION FOR GROUPS 1, 3 AND 5 COMBINED, GROUPS 2, 4 AND 6 COMBINED, AND FOR THE TOTAL SAMPLE

Stim.		*Aud. errors*	*Ass. errors*	*Rand. errors*	*D. K.*	*Total*
Groups 1, 3 and 5 combined (N 51) (Patients with visual involvement)						
Aud.	N	42	100	22	20	184
	M	·82	1·96	·43	·39	3·61
Comb.	N	31	90	18	8	147
	M	·61	1·76	·35	·16	2·88
% reduction		26%	10%	18%	60%	20%
Groups 2, 4 and 6 combined (N 14) (Patients without visual involvement)						
Aud.	N	6	29	0	2	37
	M	·43	2·07		·14	2·64
Comb.	N	4	13	0	1	18
	M	·14	1·14		·07	1·36
% reduction		33%	55%		50%	51%
Total Sample (N 67)						
Aud.	N	48	134	22	22	226
	M	·72	2·00	·33	·33	3·37
Comb.	N	35	105	18	9	167
	M	·52	1·57	·27	·13	2·49
% reduction		27%	22%	18%	59%	26%

which patients will not be able to do so, since patients were not classified on the basis of the present test.

Table III shows the percentage of each kind of error made by patients grouped according to the total errors made on each presentation, and on the two presentations combined. Patients ranked as making zero errors made no errors on one presentation but did on the other. Here

TABLE III.—PERCENTAGE OF ERROR TYPES ON AUDITORY RECOGNITION FOR PATIENTS GROUPED ACCORDING TO TOTAL ERRORS

Stim.	*Errors*	*N. patients*	*Aud. errors*	*Ass. errors*	*Rand. and Total D. K.*	*Total errors*
Aud.	0	2				0
	1	19		100%		19
	2–3	24	21%	72%	7%	61
	4–6	13	15%	72%	13%	61
	7–9	5	22%	44%	34%	41
	10–12	4	39%	20%	41%	44
Total		67	21%	59%	20%	226
Comb.	0	15				
	1	24	8%	92%		24
	2–3	13	12%	85%	3%	33
	4–6	7	14%	67%	19%	36
	7–9	5	28%	45%	28%	40
	10–13	3	38%	38%	24%	34
Total		67	21%	63%	16%	167
Both presentations combined	1	14		100%		14
	2–3	17	7%	91%	2%	44
	4–6	19	19%	77%	4%	96
	7–14	8	15%	64%	21%	80
	15–25	9	31%	38%	19%	159
Total		67	21%	61%	18%	393

it can be seen again that association errors constitute the "best" errors; if a patient makes only one error it will almost certainly be an association-type error. In general the more errors a patient makes, the more random and "don't know" responses there will be. Auditory errors are less predictable on the basis of total score. The probability is that this kind of auditory confusion does not reflect a general language reduction in most cases, but rather a perceptual deficit, a partial auditory imperception found in some patients but not in others.

Findings reveal a reduction of vocabulary in auditory recognition. Errors are of three classes: (1) confusion of words closely associated in meaning; (2) confusion of words similar in sound; and (3) random and "don't know" responses.

XUM

When the stimulus is strengthened by the addition of a visual cue, errors decrease in general, but decrease most for those patients who are able to utilize the added visual cue to the best advantage.

Association errors are the most common, and constitute the greatest proportion of the errors of patients with mild impairment. Auditory confusions occur on all levels except perhaps the very mildest, and appear to represent a specific impairment of auditory perception. Random errors tend to occur only in the most severely impaired patients.

Reduction of Naming Vocabulary

Previous studies have shown that naming, which involves recall, as well as a finely co-ordinated motor response, is a much harder task for aphasic patients than pointing to objects named by the examiner, which involves only recognition and pointing (Schuell and Jenkins, 1959).

A test was constructed consisting of 18 cards, each containing a picture of a common object, and the name of the object in print. Words were all taken from the first thousand most commonly used words in the English language (Thorndike and Lorge, 1944), and were all words used on the Kent-Rosanoff Word Association Test, for which the popular responses of normal populations are known (Russell and Jenkins, 1954). Words used were baby, bread, chair, yellow, hand, street, head, table, boy, green, house, sheep, window, girl, blue, bed, man and red. The patients was asked to look at the card and name the picture.

The test was administered to a non-selected series of 92 aphasic patients. 24 patients made no errors; 8 were judged untestable because no responses could be secured. Data consist of 487 errors, out of 1,080 responses made by the remaining 60 patients.

Errors were classified as association errors, approximations, and irrelevant and "don't know" responses.

Only errors clearly associated with the stimulus in meaning were classified as association errors. Most of these were popular responses, such as *boy* for *girl*, *green* for *red*, and *door* for *window*. A few were personal associations such as *Lisa* (the patient's daughter) for *girl*. Questionable associations such as *dig* for *girl* were classified as irrelevant.

Intelligible but defective responses (such as *dirl* for *girl*, or *boo* for *blue*) were classified as approximations. Mispronunciations which are recognizable attempts to pronounce the correct word are made by two groups of patients, those whose auditory feedback or auditory recall is imperfect, and those whose motor control is defective. Clinically these errors can be distinguished by the consistency of the motor errors (the same sounds tend to be consistently defective). For example, *wed* for *red* is an error which occurs frequently when patients have difficulty pronouncing initial "r." To take a different example from the present data, *timble* for *table* involves more complex co-ordinations than the correct word,

and is probably an auditory inaccuracy. In addition to the inconsistency, auditory errors can usually be corrected readily by ear, while motor or sensorimotor errors tend to be more resistant. However, no attempt has been made to distinguish between the two types of mispronunciations here, since this involves detailed study of the overall speech pattern of each patient.

Irrelevant responses consisted of jargon, perseverative responses and occasional irrelevant words; these were combined with no response, for the purposes of this analysis.

Data here, like those for word recognition above, were contaminated by inclusion of patients who had received intensive treatment as well as patients who had received none.

Table IV shows the number, mean number and percentage of each kind of error for the clinical groups previously described and for the entire sample. 29 per cent of total errors were association errors, 19

TABLE IV.—FREQUENCY OF ERROR TYPES IN NAMING FOR CLINICAL GROUPS AND TOTAL SAMPLE

Group	*N*		*Association errors*	*Approximation errors*	*D. K. and irrelevant*	*Total*
Group 1	5	N	5	20	52	77
		M	1·00	4·00	10·40	15·40
		%	6%	26%	68%	100%
Group 2	6	N	8	6	9	23
		M	1·33	1·00	1·50	3·83
		%	35%	26%	39%	100%
Group 3	6	N	18	3	3	24
		M	3·00	·50	·50	4·00
		%	75%	12·5%	12·5%	100%
Group 4	8	N	32	6	33	71
		M	4·00	·75	4·13	8·88
		%	45%	8%	47%	100%
Group 5	29	N	57	50	98	205
		M	1·97	1·72	3·38	7·07
		%	28%	24%	48%	100%
Group 6	4	N	16	5	43	64
		M	4·00	1·25	10·75	16·00
		%	25%	8%	67%	100%
Unclass.	2	N	7	2	14	23
Total	60	N	143	92	252	487
		M	2·38	1·53	4·20	8·12
		%	29%	19%	52%	100%

per cent were approximations, and 52 per cent were irrelevant or "don't know" responses.

Comparisons between the clinical groups are not very meaningful because of the small number of patients in some groups. In general, Group 1 patients perform a little better than expectancy for this group, probably because patients who could not perform at all were excluded.

XUM

Group 2, on the other hand, would be expected to perform more like Group 3 in this sample if this were a characteristic distribution of Group 2 patients. Here it included two patients who made eight errors each, one who made four, and three who made one error apiece. In Group 4 more approximation errors would be expected; these are probably obscured first by the fact that patients who had received treatment had mastered most common monosyllabic words, and secondly by the large proportion of unintelligible or "don't know" responses made by the more severe patients in the group.

Table V shows that if Group 6 is excluded, the order of severity for the clinical groups is about the same for naming as for auditory recognition.

TABLE V.—MEAN NUMBER OF ERRORS FOR CLINICAL GROUPS AND TOTAL SAMPLE ON WORD RECOGNITION (AUDITORY STIMULUS) AND NAMING TESTS

	Word recognition mean	*Naming mean*
Group 1	6·16	15·40
Group 4	3·50	8·88
Group 5	2·69	7·07
Group 2	2·00	3·83
Group 3	2·00	4·00
Total sample	3·48	8·12

Group 6 patients ranked third in order of severity (M=2·75) on word recognition, and most severe on naming (M=16). These are patients who have partial auditory imperception, with retention of some appropriate spontaneous speech. The extreme difficulty such patients have naming and giving specific information, even when they understand what is desired, is in marked contrast to their conversational speech, which must arise from complex patterns of environmental and internal stimuli. This discrepancy is found in no other clinical group. Theoretically, if Penfield and Roberts (1959) are correct in postulating a language integrating mechanism in the thalamus which receives impulses from auditory and visual cortical areas, such a clinical picture could result from partial interruption of these pathways, while the thalamic nuclei could still be stimulated from other sources, producing some language. The spontaneous speech of these patients while frequently fluent, well-formulated and appropriate is by no means intact. One Group 6 patient receiving treatment at present frequently tells his clinician, "You tell me it's right, but I don't know what I said." At the same time he frequently knows when his response is wrong.

In Table VI, patients in Groups 1, 4 and 5, all of whom have a motor or sensorimotor defect are combined, and compared with patients in

TABLE VI.—FREQUENCY OF ERROR TYPES IN NAMING FOR CLINICAL GROUPS 1, 4 AND 5 AND GROUPS 2, 3 AND 6 COMBINED

N		*Association errors*	*Approximation errors*	*Irrelevant and "don't know"*	*Total*
		Groups 1, 4 and 5 combined (Patients with motor involvement)			
42		94	76	183	353
	M	2·24	1·81	4·36	8·40
	%	27%	21%	52%	100%
		Groups 2, 3 and 6 combined (Patients without motor involvement)			
16		42	14	55	111
	M	2·63	·88	3·44	6·94
	%	38%	13%	49%	100%
		Total sample (58*)			
58		136	90	238	464
	M	2·34	1·55	4·10	8·00
	%	29%	20%	51%	100%

*Two unclassified patients omitted.

Groups 2, 3 and 6 who have no specific motor problems, although they mispronounce words because of defective auditory feedback and recall. In spite of this, patients in the first three groups make more approximation errors, as would be predicted, both when means and percentages of approximation errors are compared.

In Table VII types of naming errors are compared with total errors ranked in order of magnitude. Here it can be seen again that in general there is an inverse relationship between association errors and total errors, and a positive one between total errors and irrelevant or "don't

TABLE VII.—FREQUENCY OF TYPES OF NAMING ERRORS COMPARED WITH TOTAL ERRORS

Total errors	*N*	*Association errors*	*Approximation errors*	*D. K. and irrelevant*	*Total*
1	12	9	1	2	12
		75%	8%	17%	M 1·0
2–4	9	12	10	1	23
		52%	44%	4%	M 2·25
5–7	7	19	5	15	39
		49%	13%	38%	M 5·57
8–10	11	44	15	37	96
		46%	16%	38%	M 8·73
11–15	11	37	35	76	148
		25%	24%	51%	M 13·45
16–18	10	22	26	121	169
		13%	15%	72%	M 16·90
Total	60	143	92	252	487
		29%	19%	52%	M 8·12

know" responses. Approximation errors, on the other hand, are less predictable on the basis of total score, since they reflect specific kinds of impairment which are present in some patients and not in others, and which may be of any degree of severity, from mild to extremely severe.

Reduction of Reading Vocabulary

A test was constructed consisting of 30 sets of paired words. Ten pairs were popular associations, such as desk–chair, window–door and stand–sit. Ten pairs were words which sound alike but do not look alike, such as pies–buys, bed–said and blow–sew. The last ten pairs were words which look alike but do not sound alike, such as horse–house, bear–hear and bank–bark.

Two presentations of the test were made to each subject. For the visual presentation each card contained a picture of the test object, with the two printed words below, and the subject was required to point to the word which matched the picture. For the auditory presentation each card contained the two words of the pair, and the subject was asked to point to the word spoken by the examiner. Association, visual and auditory pairs were randomized for presentation, and the two forms of the test were administered on different days.

The test was administered to 21 aphasic patients. This cannot be considered a representative sample. It consisted of 13 Group 5 patients, 4 Group 3 patients, 2 Group 6 patients, and 2 patients who were not classified because they were not considered neurologically stable.

Findings

Table VIII shows the number, mean number and percentage of each type of error made by 21 patients on each type of presentation, with combined errors for both presentations.

Table VIII.—Number, Mean and Percentage of Types of Reading Errors

		Matching Word to Picture			
N		*Visual errors*	*Auditory errors*	*Association errors*	*Total errors*
21	N	17	12	31	60
	M	·81	·57	1·48	2·86
	%	28%	20%	52%	100%
		Printed to Spoken Word			
21	N	24	9	19	52
	M	1·14	·43	·90	2·48
	%	46%	17%	37%	100%
		Combined errors: both presentations			
21	N	41	21	50	112
	M	1·95	1·00	2·38	5·33
	%	36%	19%	45%	100%

The fact that more errors were made matching words to pictures than matching printed to spoken words is considered an artifact of this sample. There is a similar test on the Minnesota Test for Differential Diagnosis of Aphasia, except that error types are not differentiated and precise discriminations are not required. Unpublished data from an exploratory study which tabulated results for 131 aphasic patients shows a reversal of this finding. 41 per cent of this sample made errors matching printed to spoken words, with a mean error of 5·13, while 31 per cent of these patients made errors matching words to pictures, with a mean error of only 1·65.

However the present data are sufficient to show a reduction of reading vocabulary, even on very common words, and the presence of both association errors and perceptual confusions.

Table IX shows that even in this small sample all patients do not perform alike. 8 patients made more errors matching words to pictures than matching printed to spoken words, which is a reversal of the usual finding. It can be seen that the spoken word helped the patients considerably to identify the correct word, reducing auditory errors by 75 per cent, association errors 57 per cent, visual errors 30 per cent, and total errors 53 per cent. This would seem to indicate that for these patients visual processes were too impaired to permit the necessary discriminations and recognitions to function adequately without assistance from another sensory modality.

Six patients made more errors matching printed to spoken words than matching words to pictures. Depriving these patients of the information presented by pictures and forcing them to depend on the spoken word *increased* visual confusions 500 per cent, auditory errors 50 per cent and total errors 90 per cent, while association errors decreased 33 per cent. The 50 per cent increase and the 33 per cent decrease are probably not significant, since they represent differences of only one and two errors respectively, spread over 6 patients. What is significant is that these patients made six times as many errors identifying words spoken by the examiner as matching the same words to pictures, pointing to more severe auditory than visual involvement.

Seven patients made an equal number of errors on both presentations. The number of visual errors remained exactly the same; auditory errors decreased by two, and visual errors increased by two when the spoken word was presented. The latter differences are probably not significant.

The sample was considered too small for further analysis.

Reduction of Writing Vocabulary

The following 20 spelling words are a part of the Minnesota Test for Differential Diagnosis of Aphasia, administered to all patients on admission to the Aphasia Clinic: bed, car, chair, clock, house, table, boy,

TABLE IX.—PERCENTAGE OF REDUCTION OR INCREASE OF READING ERRORS ON MATCHING PRINTED TO SPOKEN WORDS

	Word to picture				*Printed to spoken word*				*Combined errors*			
Type of error	*Visual*	*Auditory*	*Associa-tion*	*Total*	*Visual*	*Auditory*	*Associa-tion*	*Total*	*Visual*	*Auditory*	*Associa-tion*	*Total*
1. *Patients Who Made More Errors Matching Word to Picture* (*N* 8)												
No. errors	10	8	14	32	7	2	6	15	17	10	20	47
M	1·25	1·00	1·75	4·00	·88	·25	·75	1·88	2·13	1·25	2·50	5·88
%	31%	25%	44%	100%	47%	13%	40%	100%	36%	21%	43%	100%
% reduction or increase					−30%	−75%	−57%	−53%				
2. *Patients who made more errors matching printed to spoken word* (*N* 6)												
No. errors	2	2	6	10	12	3	4	19	14	5	10	29
M	·33	·33	1·00	1·67	2·00	·50	·67	3·17	2·33	·83	1·67	4·83
%	20%	20%	60%	100%	63%	16%	21%	100%	48%	17%	35%	100%
% reduction or increase					+500%	+50%	−33%	+90%				
3. *Patients Who Made Equal Total Errors* (*N* 7)												
No. errors	5	2	11	18	5	4	9	18	10	6	20	36
M	·71	·29	1·57	2·57	·71	·57	1·29	2·57	1·43	·86	2·86	5·14
%	28%	11%	61%	100%	28%	22%	50%	100%	28%	17%	55%	100%
% reduction or increase					0	+100%	−18%	0				
4. *Total* (N 21)												
No. errors	17	12	31	60	24	9	19	52	41	21	50	112
M	·81	·57	1·48	2·86	1·14	·43	·90	2·48	1·95	1·00	2·38	5·33
%	28%	20%	52%	100%	46%	17%	37%	100%	36%	19%	45%	100%
% reduction or increase					+41%	−25%	−39%	−13%				

XUM

dog, bread, apple, paper, grass, man, has, rain, watch, yellow, country, business and necessary. For the first six words the patient is asked to write the name of a picture; the rest are written to dictation. Words were selected from grades 2 to 6 on graded spelling lists. From a test series of 157 patients tested on the Research Edition of the Minnesota Test (1955), all the original spelling papers contained in the files were extracted for patients in Groups 2, 3 and 4. To these were added the records of the first 10 patients in Group 1 and the first 15 patients in Group 5 whose original papers were on file, making a series of 79 papers for analysis.

All errors were tabulated and classified as follows:

(1) No response, or no appropriate response. Responses judged not appropriate were illegible responses, perseverative responses and meaningless combinations of letters such as NEL for clock.

(2) Association errors, such as *green* for *grass* and *home* for *house*. Recognizable approximations of associated words were also included in this category, such as *tabe* for *bed* and *flr* for *bread*.

(3) Visual confusions. These consisted of distortions and reversals of letter forms, confusions of letters with similar visual configurations, such as *bog* for *boy*, *match* for *watch*, and *howse* for *house*. Phonetic spellings were also included in this category, since these are characteristic of patients with visual impairment on a cerebral level (Schuell, 1954); examples from the data are *bisness* for *business*, *boe* for *boy*, and *bred* for *bread*.

(4) Auditory confusions, consisting of substitution of words which sounded like the given word, such as *red* for *bread* and *hair* for *chair*.

(5) Proprioceptive confusions. A tendency had been observed for patients with sensorimotor impairment to confuse sounds with similar articulatory positions and movement patterns, such as *pbm* made on the lips, *tdnl* with the tongue tip touching the teeth ridge, *fv*, *kg*, *rl*, and so on; therefore this category was included. Examples found were *apper* for *apple*, *bet* for *bed*, *taben* for *table*, *chail* for *chair*, et cetera.

(6) Approximations. These were misspellings in which at least a part of the given word was correct. Errors were omissions of letters, reversals of letter sequences, letter substitutions and so on. Examples of words classified as approximations were *buisness*, *grss*, *chur*, *yellew*.

Since it is impossible to know what was going on in the patient's mind when he wrote a word, it is of course probable that there are misclassifications. However, it was possible to consider errors in the context of the overall performance of each patient, which made judgments more reliable, since patients tend to show consistency in the kinds of errors they make.

XUM

Findings

The number, mean number and percentage of each error type for each clinical group and for the total sample are found in Table X.

TABLE X.—NUMBER, MEAN AND PERCENTAGE OF ERROR TYPES ON SPELLING FOR CLINICAL GROUPS AND TOTAL SAMPLE

		No response	*Association errors*	*Visual errors*	*Audio errors*	*Proprio. errors*	*Approx. errors*	*Total*
Group 1	N	190	0	2	0	2	4	198
(N 10)	M	19·00		·20		·20	·40	19·80
	%	96%		1%		1%	2%	
Group 2	N	23	6	3	1	1	17	51
(N 18)	M	1·27	·33	·17	·06	·06	·94	2·83
	%	45%	12%	6%	2%	2%	33%	
Group 3	N	92	15	75	3	3	41	229
(N 23)	M	4·00	·65	3·26	·13	·13	1·78	9·96
	%	40%	7%	33%	1%	1%	18%	
Group 4	N	56	10	8	0	5	27	106
(N 13)	M	4·31	·77	·62		·38	2·08	8·15
	%	53%	9%	8%		5%	25%	
Group 5	N	64	3	41	1	2	38	149
(N 15)	M	4·27	·20	2·73	·07	·13	2·53	9·93
	%	43%	2%	27%	1%	1%	26%	
Total	N	425	34	129	5	13	127	733
Sample	M	5·38	·43	1·63	·06	·16	1·61	9·27
(N 79)	%	58%	5%	17%	1%	2%	17%	

The high percentage of no response or no appropriate response is characterististic of severely impaired patients, as is indicated by the fact that 95 per cent of the errors of Group 1 were of this class. It is also characteristic of some patients in other groups who have received no treatment for aphasia. Many aphasic patients can write so little at the time of initial testing that error patterns cannot be studied until more performance can be obtained. However, several findings are of interest in Table X. Group 1 patients are chiefly notable for lack of performance on writing tasks. Patients in Group 2 perform a good deal better than patients in any other clinical group, as can be seen from a comparison of the mean number of total errors for all the clinical groups. They made three visual-type errors; one was a reversal, one a confusion of two similar letters, and one a phonetic spelling. Actually, any patient beginning to write with the nonpreferred hand may produce an occasional reversal. A diagnosis of visual impairment was not made unless such types of errors occurred frequently, were persistent and characterized all samples of the patient's writing.

Whereas on word comprehension and naming, Group 3 patients performed much like Group 2 patients, showing a comparable amount of language reduction, on writing comparatively easy words they averaged

three and a half times as many total errors and more than 19 times as many visual errors. Group 5 patients who also show some visual involvement, had the second highest mean number and percentage of visual confusions.

Group 4 patients who have sensorimotor involvement showed the highest percentage of proprioceptive confusions, but the number cannot be considered significant. This was predictable, for such errors do not usually appear until patients have acquired functional vocabulary, and been taught phonetic techniques as an approach to reading and writing. They tend to be striking through the learning period, then gradually decrease in all modalities.

Discussion

Data have been presented which show reduction of vocabulary in aphasia appearing in all language modalities. The same kinds of errors tend to appear, whether patients are asked to point to objects named by the examiner, to name objects, match words to pictures, match spoken to printed words or write words to dictation.

Confusions of words which are associated in meaning or experience are common to all modalities. Aphasic patients who misname objects frequently use the same words that normals use when asked to respond to a word with the first word they think of (Schuell, 1950). These are, of course, learned associations. It would appear that as we learn language, verbal symbols become linked not only to specific objects of certain sizes, shapes, colours and other attributes, but generalized to some extent to total situations and to concepts of many degrees of complexity, to which many other verbal symbols also become linked. Hebb has tried to provide a neurological basis for this kind of learning with his theories of reverberating circuits and cell assemblages (Hebb, 1949). In children learning to talk, in states of fatigue and inattention, and much more severely in aphasia, it is as though given stimuli activate only parts of these clusters. Clinically this seems to be true. When patients are being trained to recognize individual sounds and hear them in words, they are usually able to give only one word which begins with a given sound at first; later the same simulus may produce two or three, or four or five different words. The same kind of performance results when patients are asked to respond to a stimulus word with whatever they think of. One patient who had travelled in many parts of the world, was asked to respond thus to *India*. He said only *women*. Later, to the same word he said, "Ganges, river, stones, women washing clothes." Similar processes sometimes occur when patients are searching for particular words to convey their thoughts. One patient, trying to tell what kind of a car he had, went on something like this, "Ford, no, Dodge, no, Chevy, no, Plymouth, that's it, that's right. I got a new Plymouth."

XUM

While present knowledge does not permit description of the neurological mechanisms involved in such complex cerebral processes as language, it is becoming increasingly clear that simple associative processes such as those described here play an important part in many aspects of normal language behaviour. Experimental studies performed in the last ten years have shown that a variety of functions such as recall (Jenkins, Mink and Russell, 1958), learning (Russell and Storms, 1955), transfer (Ryan, 1957) and generalization (Mink, 1957) may be mediated by such linkages. The importance of these processes in normal language is in close accord with the findings presented here regarding associative errors in aphasia. As vocabulary breaks down in aphasia, those association processes still intact serve to mediate the errors which appear. At more severe levels of vocabulary deficit, association processes themselves begin to break down, and errors of more remote origin manifest themselves. At the most severe levels of deficit, errors become even more irrelevant, finally becoming random or "no response" errors.

The effects of auditory, visual, sensorimotor and motor impairment on language can also be observed in aphasia. Some of these defects produce a much greater deficit in one modality than another; writing is more dependant on visual processes, for example, than is comprehension or speech; speech is more dependent upon complex motor co-ordinations than is comprehension or silent reading. In some aphasic patients visual processes are intact, but reading and writing suffer varying degrees of impairment from the effects of the general language deficit which is present, of which reduction of vocabulary is one aspect.

Summary

Data have been presented which show that reduction of vocabulary in all modalities is characteristic of language impairment in aphasia. Further, the similarities between errors observed in recognizing spoken words, naming, matching printed words to pictures, matching printed to spoken words and writing words to dictation are considered evidence of a language deficit independent of modality and of the recurring patterns of clinical symptoms found in aphasic patients. At the same time, other kinds of errors reflecting specific perceptual, motor and sensorimotor involvement present in some patients and not in others, were found to impair performances differentially in various modalities and in the diagnostic groups described.

This research was done during the tenure of an NIH research grant by the senior author. Some of the computational work was done by Joanne D'Andrea, as a research assistant employed by funds from this grant. The reading tests were constructed by Lydia Landis, member of the staff of the Aphasia Clinic, Minneapolis VA Hospital. Tests were administered by the senior author, Amy Bricker, Virginia Carroll, Lydia

XUM

Landis, Jayne Nelson, Ruby Simmons and Barbara Street, members of the staff of the Aphasia Clinic at various period since 1955.

REFERENCES

FREUD, S. (1953) "On Aphasia." New York.

GUTTMAN, L. (1947) *Educ. Psychol. Measmt.*, **7**, 247.

HEAD, H. (1926) "Aphasia and Kindred Disorders of Speech." New York.

HEBB, D. O. (1949) "The Organization of Behaviour." New York.

JENKINS, J. J., MINK, W. D., and RUSSELL, W. A. (1958) *Psychol. Rept.*, **4**, 127.

KENT, G. H., and ROSANOFF, A. J. (1910) *Amer. J. Insanity*, **67**, 37 and 317.

MINK, W. D. (1957) "Semantic Generalization as Related to Word Association." Minneapolis.

PENFIELD, W., and ROBERTS, L. (1959) "Speech and Brain-Mechanisms." Princeton.

RUSSELL, W. A., and JENKINS, J. J. (1954) "The Complete Minnesota Norms for Responses to 100 Words from the Kent-Rosanoff Word Association Test." Minneapolis.

——, and STORMS, L. H. (1955) *J. exper. Psychol.*, **49**, 287.

RYAN, J. J. (1957) "An Experimental Comparison of Response Transfer Facilitated by Meaningfully Similar and Associated Verbal Stimuli." Minneapolis.

SCHUELL, H. (1950) *J. Sp. and Hear. Dis.*, **15**, 291.

—— (1954) *Neurology*, **4**, 179.

—— (1955*a*) "The Minnesota Test for Differential Diagnosis of Aphasia." Research Edition, Minneapolis.

—— (1955*b*) *A.M.A. Arch. Neurol. Psychiat.*, **74**, 308.

——, and JENKINS, J. J. (1959) *Psychol. Rev.*, **66**, 45.

THORNDIKE, E. L., and LORGE, I. (1944) "The Teachers Word Book of 30,000 Words." New York.

WEISENBURG, T. H., and MCBRIDE, K. E. (1935) "Aphasia, a Clinical and Psychological Study." New York.

WEPMAN, J. M., and JONES, L. K. (1958) "The Production and Demonstration of a Primary Language Abilities Test for Aphasia." Chicago.

XUM

THE ÆTIOLOGY AND NEUROLOGICAL COMPLICATIONS OF RETINAL VASCULITIS

BY

RICHARD H. R. WHITE[1]

(*From the United Bristol Hospitals*)

ALTHOUGH Eales (1880, 1882) first described a syndrome of recurrent intra-ocular hæmorrhages in young men, his observations were evidently limited, for the fundamental vascular abnormalities (Plate XXVII), which are now known to cause these recurrent vitreous and retinal hæmorrhages, are not described in his papers. They were, however, well recognized by Axenfeld and Stock (1911), who used the term periphlebitis to describe the white sheaths which are seen characteristically running alongside the retinal veins. The term *retinal vasculitis*, which is more completely descriptive, was introduced by Ballantyne and Michaelson (1937; 1947) and is based upon their histological findings in an eye excised on account of secondary glaucoma. Microscopical sections showed perivascular round cell infiltration which occluded vessels both by external pressure and by direct invasion of the lumen, causing intravascular thrombosis and hæmorrhage from the weakened vessel wall.

A variety of neurological abnormalities have been reported in association with retinal vasculitis. Finnoff (1921) described a patient who developed a progressive paraplegia from the age of 14 years and began to have vitreous hæmorrhages at 30 years. Marchesani and Stauder (1935) observed various neurological abnormalities in 6 patients, including 2 hemiplegias and 2 cases of multiple sclerosis. These patients also had evidence of peripheral vascular disturbance and in one an autopsy diagnosis of "probable cerebral thrombo-angiitis obliterans" was made. Rucker (1945) collected 50 patients showing perivenous sheathing—without intra-ocular hæmorrhages, however—and found that multiple sclerosis had been diagnosed in 31 and suspected in a further 11, "by a competent neurologist." He remarked that "The fundal picture bears a resemblance to a feature observed by a number of pathologists in their sections of the central nervous system of persons who have died of multiple

[1]Present address: Makerere College Medical School, Mulago Hospital, P.O. Box 2072, Kampala, Uganda.

sclerosis, namely an accumulation of cells around venules . . ." However, the lymphocytic cuffing of the Virchow-Robin spaces found in some cases of acute disseminated sclerosis (Greenfield, 1958) is unlike the perivenous infiltration with mononuclear and epithelioid cells (Ballantyne and Michaelson, 1937) and occasional giant cells (Axenfeld, 1920; Verhoeff and Simpson, 1940) which is seen in retinal vasculitis. Moreover, Greenfield (1958) states that it is not the primary lesion of disseminated sclerosis but follows myelin destruction and microglial proliferation in the parenchyma. Retinal nerve fibres are not myelinated and the perivenous sheathing seen in Eales' disease appears to be the primary lesion. Wybar (1952) also observed perivenous sheathing in 9 out of 91 cases of disseminated sclerosis. The fact that neither his nor Rucker's patients had intra-ocular hæmorrhages suggests that the nature of the sheathing in these cases differs from that associated with Eales' disease.

Silfverskiöld (1947) gave an excellent description of 3 patients who developed transverse spinal cord lesions, with gradual but incomplete recovery, while their retinal vasculitis was active. All 3 patients showed a rise of cells (mainly lymphocytes) and protein in the cerebrospinal fluid. Veirs (1948) reported 4 cases of retinal vasculitis with intra-ocular hæmorrhages and neurological involvement. Case 1 had papillœdema and intention tremor, with increased cells and protein in the cerebrospinal fluid. He later developed a right hemiplegia, with aphasia and dysphagia, but gradually recovered. Case 2 had papillœdema but was also hypertensive, and Case 3 had headaches only. In Case 4 the peripheral neuritis, headaches, nausea and attacks of coma could well be attributed to longstanding diabetes mellitus with renal glomerulosclerosis, hypertension and uræmia. Jefferson and Cloake (1952) denied the existence of neurological complications and suggested that, in previously reported cases, either the neurological findings were coincidental or the diagnosis of Eales' disease was incorrect. They did not state whether the cerebrospinal fluid had been examined in any of their 6 cases. Miller (1958) has described the case of a woman who had recurrent vitreous hæmorrhages in 1942 (aged 26 years), 1949 and 1957, and developed her first attack of what was clinically disseminated sclerosis in 1950.

The purpose of this paper is to describe the clinical and laboratory findings in 17 patients who were investigated and followed up between October 1954 and December 1959, and to discuss the ætiology of retinal vasculitis and its relation to disorders of the central nervous system. A brief note on the course of the disease is included.

Material and Methods

10 of the 17 patients were either new or currently attending hospital on account of visual disturbance. The remaining 7 had ceased to attend and were asked to return for the purpose of the present inquiry. All 17 patients were examined personally but only 13 permitted complete investigation. Where appropriate, investigations previously

XUM

carried out upon the remaining 4 patients have been included in the series. In an attempt to obtain as much information as possible about this obscure condition, a wide range of investigations was planned and many have produced normal results.

Hæmatological investigations completed upon each of 15 patients consisted of hæmoglobin percentage, hæmatocrit, total and differential white cell count, erythrocyte sedimentation rate, platelet count, bleeding and clotting times and prothrombin index. Direct eosinophil counts were recorded in 14 patients and blood groups in 13. Biochemistry included differential serum protein estimations (14 patients), liver function tests (12), serum calcium and inorganic phosphate (10). Serology consisted of Wassermann and Kahn reactions (15) and Brucella agglutination tests (13). Urine from all 17 patients was examined for the presence of albumin, sugar and abnormal cellular deposits. All patients had chest radiographs.

Dermal sensitivity to tuberculin, brucellin, histoplasmin and coccidioidin was determined in most of the patients. With the exception of Cases 5 and 11, who refused further investigation, all the tests were carefully made, personally, with intradermal injections of 0·1 ml of antigen, and read after forty-eight, seventy-two and ninety-six hours, thus minimizing observer error. With tuberculin, dilutions of 1/100,000, 1/10,000 and 1/1,000 (corresponding to 0·1, 1·0 and 10 tuberculin units in 0·1 ml of solution) were used. The remaining tests were made with dilutions of 1/100. Erythema and induration of not less than 5 mm. diameter, persisting for forty-eight hours or more, constituted a positive reactions in all the tests and, in the case of brucellin, the classification proposed by Harris (1950) was used in recording the tests.

Cerebrospinal fluid, obtained by lumbar puncture from 16 patients, was cultured and analysed microscopically and chemically. A lumbar puncture was not performed upon patient No. 17, who refused full investigation.

In view of reported cases of sarcoidosis (von Bahr, 1938) and brucellosis (Foggitt, 1954), and in the light of some of the findings in the present series, percutaneous liver biopsy was performed in 9 patients who gave consent. The procedure was carried out under local analgesia, by standard technique (Terry, 1949) and no post-operative complications were encountered.

Clinical and Laboratory Findings

Incidence (Table I).—There were 14 men and 3 women in this series; the apparent age of onset ranged from 17 to 48 years. Disease was bilateral in 4 patients and, in all, 8 right and 13 left eyes were affected. Arteries were involved in only one case. 8 patients had one or more episodes of total loss of vision in the affected eye, owing to the occurrence of large vitreous hæmorrhages. 14 had recurrent retinal, pre-retinal and vitreous hæmorrhages which usually caused partial interference with vision but were sometimes found on routine inspection during clinic attendances. 9 patients developed retinitis proliferans (Plate XXVII), a complication in which fibrous tissue and new blood vessels invade the vitreous humour as a result of organization of incompletely absorbed vitreous hæmorrhage. There was associated uveitis in 3 cases, affecting 4 eyes.

No constant occupational or social factors were observed (Table I). A previous history of epistaxis was obtained in only 5 cases and there were no instances of abnormal bruising or bleeding tendency. There was no evidence of peripheral vascular disease or of mucocutaneous ulceration in any of the patients. Outside the central nervous system the history and

PLATE XXVII

Fundus painting of left eye of patient No. 1, showing extensive perivenous sheathing (A) and numerous retinal hæmorrhages (B) in the periphery, a fresh pre-retinal hæmorrhage (C) and a recent, partly absorbed vitreous hæmorrhage (D).

To illustrate article by Richard H. R. White.

XUM

PLATE XXVIII

Fundus painting of left eye of patient No. 3, showing retinitis proliferans, with fibrous tissue (A) and new blood vessels (B). This has spared the macula, causing no residual impairment of sight.

To illustrate article by Richard H. R. White.

physical examination were negative except in patient No. 14, whose case is of sufficient interest to be worth recording separately.

TABLE I.—SEX, AGE, OCCUPATION AND CLINICAL DETAILS OF 17 PATIENTS WITH RETINAL VASCULITIS

Patient No.	*Sex*	*Age at onset*	*Occupation*	*Eye affected*	*Veins/arteries?*	*Gross vitreous h'ge*	*Smaller haemorrhages*	*Retinitis proliferans*	*Uveitis*	*C.N.S. signs*	*C.S.F. changes*	*Other disorders*
1	M	29	Labourer	RL	V	+	+	+			+	Active tuberculosis
2	M	23	Storekeeper	RL	V	+	+	+			+	Healed tuberculosis
3	F	39	Housewife	L	V	+	+	+				
4	M	48	Electrician	R	V		+					
5	M	17	Clerk	L	V		+		RL			
6	M	37	Schoolmaster	L	V		+			+		
7	M	24	Plasterer	L	V	+		+				
8	M	34	Manager	R	V		+	+				Sinusitis
9	F	30	Housewife	L	V		+	+		+	+	Recurrent headache
10	F	39	Housewife	R	V	+	+			+		
11	M	21	Engineer	L	V		+					
12	M	29	Fitter	RL	V	+	+	+				Quiescent tuberculosis
13	M	43	Bus conductor	L	A	+						
14	M	28	Salesman	L	V		+	+	R			Recent brucellosis
15	M	34	Labourer	R	V		+		R	+	+	
16	M	21	Signalman	R	V		+				+	
17	M	29	Engineer	RL	V	+	+	+				

Patient No. 14, *male, born* 1926. He was well until 1945 when he had two unexplained febrile illnesses. He admitted having previously drunk raw milk in Normandy. When seen in 1955, aged 29 years, he complained of occasional lassitude but there were no abnormal physical signs apart from retinal vasculitis and early retinitis proliferans in the left eye, and signs of previous iridocyclitis in the right eye. The Mantoux test was positive at 1/10,000. The brucella agglutination test was initially negative but showed a significant rise of titre ten days after a violently positive brucellin intradermal reaction. In December 1959 he had a further febrile illness accompanied by multiple joint swellings and was found to have a positive L.E.-cell phenomenon in his peripheral blood. All other clinical and

XUM

laboratory findings, including the histology and culture of a liver biopsy specimen, were negative.

Central Nervous System (Table II).—4 patients showed abnormal physical signs in the central nervous system and 2 of them also had changes in the cerebrospinal fluid.

TABLE II.—DETAILS OF PATIENTS WITH ABNORMALITIES OF THE CENTRAL NERVOUS SYSTEM AND CEREBROSPINAL FLUID

Patient No.	*Sex*	*Retinal vasculitis*	*Other conditions*	*C.N.S. examination*	*Cerebrospinal fluid* *Cells/ c.mm*	*Protein mg%*	*Lange curve*
1	M	Severe bilateral	Active pulmonary tuberculosis	Normal	0	20	1233210000
2	M	Severe bilateral	Healed pulmonary tuberculosis	,,	19, 62, and 20	50, 60, and 65	5555431000
6	M	Mild, left	None	Residual mild paraparesis	1	20	1111000000
9	F	Mild, left	Disseminated sensory lesions; transient R. arm ataxia	Partial sensory loss, R. foot	9	20	1111100000
10	F	Proximal venous occlusion; massive intra-ocular hæmorrhages	None	Right hemiparesis	0	15	1111100000
15	M	Severe, right	Antr. and postr. uveitis (right)	Transient mild paraparesis	14	25	1111100000
16	M	Mild, bilateral	Headache, vertigo, tinnitus, deafness at onset	Normal	0	100, 50, and 30	1111100000

Patient No. 6 had previously attended the Bristol Eye Hospital in 1950 and was found to have retinal vasculitis with scattered retinal hæmorrhages in the left eye. Examination revealed exaggerated knee and ankle reflexes with bilateral extensor plantar responses. When re-examined during the present inquiry, in January 1955, these signs were still present and he also had bilateral ankle clonus. The cerebrospinal fluid was normal.

Patient No. 9 showed no neurological abnormality at the onset of intra-ocular hæmorrhages in the left eye, in 1952, but subsequently experienced transient sensory disturbances and had an episode of headache and vomiting, with ataxia of the right arm. When examined in September 1959 the only residual sign was diminished cutaneous sensation affecting the left foot. A provisional diagnosis of disseminated sclerosis was made. The

cerebrospinal fluid, examined in 1955, showed a minimal pleocytosis (9 lymphocytes per c.mm.) but not other abnormality. It was normal when re-examined in 1959.

Patient No. 10 developed a complete right hemiplegia during the puerperium in 1947 and, when admitted with gross retinal and vitreous hæmorrhages in the right eye in April 1955, was found still to have signs of a right hemiparesis, with increased muscle tone and reflexes, and impairment of fine finger movements. There was no residual muscular weakness and the plantar response on the right side was absent. In the right eye the superior temporal retinal vein was occluded proximally. The cerebrospinal fluid was normal.

Patient No. 15 was admitted with very acute retinal vasculitis together with anterior and posterior uveitis in the right eye, and was found to have greatly increased knee and ankle reflexes, with bilateral ankle clonus. There was no muscular weakness, however, and the plantar responses were flexor. The cerebrospinal fluid showed a slight rise of cell count to 14 lymphocytes per c.mm. but no other abnormality.

Three more patients showed changes in the cerebrospinal fluid without abnormal physical signs in the central nervous system. In patient No. 16 the only finding was a raised protein level and, in patient No. 1, a mildly "paretic" colloidal gold curve. In patient No. 2, however, there was a persistent rise of cellular and protein content and a strongly "paretic" Lange curve.

The cerebrospinal fluid pressure was normal in all 16 patients in whom it was examined. Chloride and sugar estimations were normal, Wassermann reactions were negative and cultures were sterile.

Hæmatology.—Two patients showed minimal eosinophilia, of doubtful significance (patient No. 4—800 per c.mm; patient No. 15—675 per c.mm). Patient No. 14 showed a postive L.E.-cell phenomenon in the peripheral blood. There were no other abnormalities. Blood groups showed the expected distribution (A–7; 0–5; B–1; Rh-positive–10; Rh-negative–3).

Biochemistry.—There were no abnormal findings.

Serology.—Following a strongly positive brucellin test, patient No. 14 showed a rise of brucella agglutinin titres from nil to 1/160 for *B. abortus* and 1/320 for *B. melitensis.* The remaining brucella agglutination tests and Wassermann and Kahn reactions were negative.

Urine.—No abnormalities were found.

Chest Radiography.—Patient No. 1 had active pulmonary tuberculosis, with cavitation, at the apex of the left upper lobe. Patient No. 2 showed a small nodular shadow at the left apex, unchanged for two years, which probably represented healed tuberculosis. Patient No. 12 showed a small area of infiltration beneath the right clavicle, which had not changed since 1950, when he had completed a course of sanatorium treatment, and which represented quiescent pulmonary tuberculosis. Patient No. 14, who had

XUM

probably had brucellosis, showed pleural thickening at the right costophrenic angle. The remaining 13 radiographs were normal.

Dermal sensitivity.—13 patients out of 15 tested (87 per cent) were tuberculin-positive (Table III). 10 exhibited sensitivity to tuberculin at dilutions of 1/10,000 or more, while only 2 gave negative reactions at dilutions of 1/1,000. Of these two, patient No. 11 gave a faintly positive reaction at 1/100, of somewhat doubtful significance.

TABLE III.—RESULTS OF DERMAL SENSITIVITY TESTS IN PATIENTS NOS. 1–15

Patient	*Old Tuberculin*			*Brucellin*	*Histoplasmin*	*Coccidioidin*
No.	1/100,000	1/10,000	1/1,000	1/100	1/100	1/100
1		−	+	−	−	−
2		−	++	++	−	−
3	−	++		−	−	−
4	−	+		−	−	−
5			−			
6	+			+	−	−
7	++			+	−	−
8	−	++		−	−	−
9		−	+	−	−	−
10	+			−	−	−
11			−			
12	−	+				
13	−	+		+	−	−
14	−	+		++++	−	−
15	−	+		++		

Of 12 brucellin tests made, 6 (50 per cent) were positive. In patient No. 14 a violent reaction occurred with central necrosis of the indurated lesion, a 5 cm. zone of erythema and œdema, ascending lymphangitis, painful axillary adenitis and pyrexia.

All 11 histoplasmin and coccidiodin tests were negative, thus reinforcing the belief that positive tuberculin and brucellin reactions represent specific sensitivity.

Liver biopsies.—All 9 specimens were adequate for histological appraisal, and showed no abnormality. Culture of the biopsy from patient No. 14 was sterile.

COURSE, TREATMENT AND PROGNOSIS

13 of the 17 patients had recurrent intra-ocular hæmorrhages over a period ranging from one to thirteen years. The remaining 4 had single episodes of bleeding; 3 of these recovered completely but 1 had residual impairment of sight owing to vitreous haze.

It is noteworthy that only 6 (29 per cent) out of 21 affected eyes eventually had completely normal vision (Table IV), whatever the treatment, although fortunately no patient had severe impairment of sight in both eyes. All the eyes showing moderate or severe impairment of sight

had interference with macular vision (Table IV) owing to the presence of retinitis proliferans or incompletely absorbed vitreous hæmorrhages in front of the macula, or a total vitreous haze. Local applications of low-voltage radiotherapy appear to give better results than other treatments or none at all (Table IV).

TABLE IV.—RESIDUAL IMPAIRMENT OF VISUAL ACUITY IN 21 AFFECTED EYES, SHOWING THE RELATION TO TREATMENT AND TO THE OCCURRENCE OF RETINITIS PROLIFERANS OR UNABSORBED VITREOUS HAEMORRAGE WHICH HAVE CAUSED INTERFERENCE WITH MACULAR VISION

		Treatment		*Interference with macular vision?*	
Visual acuity	*Total*	*Radiotherapy*	*Other/None*	*Yes*	*No*
6/4—6/6	6	3	3	0	6
6/9—6/24	9	6	3	4	5
6/36—6/60	5	1	4	5	0
Finger counting or less	1	0	1	1	0

DISCUSSION

Axenfeld and Stock (1911), Davis (1912) and Finnoff (1921) described patients with retinal vasculitis and evidence of tuberculosis. They observed focal reactions in response to subcutaneous injections of tuberculin and considered that their findings favoured a tuberculous ætiology. Axenfeld (1920) later reported finding granulomata resembling tubercles within the walls of affected retinal veins in an eye enucleated on account of secondary glaucoma. Verhoeff and Simpson (1940) also gave a detailed histological description of an enucleated eye. Sections of the optic nerve showed that the central retinal vein was occluded by an epithelioid granuloma containing giant cells of the "foreign-body" type, not characteristic of tuberculosis. Similar granulomata were found scattered among the pial and arachnoid coverings of the optic nerve. Verhoeff and Simpson (1940) quoted a similar case reported by Safár (1928) and Friedenwald (1940) referred to a third such case. In none of these cases were tubercle bacilli demonstrated in any of the sections. Gilbert (1935) made a somewhat unconvincing claim to have demonstrated acid-fast bacilli in the neighbourhood of an affected vein but his finding has not since been confirmed by other workers, and thus the most vital evidence of tuberculosis is conspicuously lacking. Haarr (1948) reported 4 cases of retinal vasculitis with primary pulmonary tuberculosis. He pointed out that the histology of retinal vasculitis is not characteristic of tuberculosis but is similar to that of erythema nodosum and suggested that the retinal vascular changes represented part of a generalized vascular response to tuberculosis.

XUM

3 patients in the present series had pulmonary tuberculosis—active, quiescent and healed—but in each case the retinal vasculitis and intraocular hæmorrhages continued after the tuberculosis had been controlled. While the overall incidence of positive Mantoux reactions (87 per cent) was normal, 67 per cent reacted to dilutions of 1/10,000 or more, suggesting that, as an ætiological agent, tuberculin-hypersensitivity is more likely than the tubercle bacillus itself.

Birnbaum *et al.* (1934) and Marchesani (1935) reported retinal perivascular sheathing in patients with thrombo-angiitis obliterous but intraocular hæmorrhages did not occur. In a careful study Schmid (1945) found no association whatever between thrombo-angiitis and Eales' disease, and the absence of evidence of peripheral vascular disease in the present series accords with his findings. Other ætiological factors which have been cited include syphilis (Finnoff, 1921), "an undiscovered blood deficiency" (Hutchinson, 1932), focal sepsis (Knapp, 1935—tonsillar; Bender, 1935—dental), allergy (O'Malley, 1944), and deficiency of essential fatty acids (Sinclair, 1956). Obvious dental sepsis was found in 2 patients in this series, 1 of whom also had chronic maxillary sinusitis, but such findings are relatively common in the population at large and may have no significance. The negative hæmatological findings preclude a hæmorrhagic diathesis. Likewise the normal erythrocyte sedimentation rates and plasma protein levels, the rarity of arterial involvement, the absence of constitutional disturbance and renal dysfunction, and the lack of response to cortisone in two patients are evidence against a generalized vascular disorder such as polyarteritis nodosa.

A positive brucellin intradermal reaction is accepted as definite evidence of sensitization to *Brucella* antigen (Dalrymple-Champneys, 1960) and it is noteworthy that 50 per cent of the tests made in this small series were positive. In all these patients the agglutination tests were negative before skin-testing and, except in one patient, the tests were not subsequently repeated. In patient No. 14, however, the agglutinins showed a significant rise of titre ten days after a violent dermal reaction. Barrett and Rickards (1953) found that some cases of chronic brucellosis initially showed negative agglutination tests and they regard a ten-fold rise of titre following a positive skin test as diagnostic. On the other hand Dalrymple-Champneys (1960) finds the evidence unconvincing. On clinical grounds it is improbable that the *Brucella* infection in patient No. 14 was active but nevertheless an ætiological relationship with retinal vasculitis seems likely. The relatively high incidence of brucellin sensitivity in this small series suggests that, as an ætiological factor, it may be at least as important as tuberculin sensitivity. The significance of the L.E.-cell phenomenon, observed in patient No. 14 during an episode of fever and polyarthritis, is not clear but it is almost certainly additional evidence of hypersensitivity.

Considered alongside reports of associated sarcoidosis (von Bahr, 1938),

primary tuberculosis (Haarr, 1948), brucellosis (Foggitt, 1954), infectious mononucleosis (Jones, 1954) and torulosis (Beck *et al.*, 1955) these observations suggest that retinal vasculitis is a non-specific tissue response to a variety of antigens, mainly bacterial. Antigens are normally destroyed in the plasma and tissue fluids by antibodies released from the reticulo-endothelial cells. If, instead, antigen-antibody reactions occur in tissue cells, they may injure those cells and provoke a local inflammatory response.

Retinal vasculitis thus seems to have something in common with another incompletely understood tissue response, erythema nodosum, which is known to occur with streptococcal and meningococcal infections, primary tuberculosis, sarcoidosis and coccidioidomycosis. It is believed that erythema nodosum is a non-specific vascular reaction to a variety of infective and toxic agents, and not a specific disease (Perry, 1944) and, as Haarr (1948) suggested, it is perhaps significant that its histological appearance (Rotnes, 1936; Lever, 1954) bears a close resemblance to those described by Axenfeld (1920), Verhoeff and Simpson (1940) and Ballantyne and Michaelson (1937, 1947) in the case of retinal vasculitis.

In the present series (Table II) 2 patients showed neurological abnormalities associated with slight cellular reaction in the cerebrospinal fluid. In patient No. 9 the pleocytosis was found two years after vitreous hæmorrhages had occurred, and preceded the development of a clinical picture resembling disseminated sclerosis by four years. In patient No. 15 the hyperreflexia in the lower limbs and the pleocytosis coincided with the onset of retinal vasculitis and uveitis.

2 patients showed neurological abnormalities with normal cerebrospinal fluid. In patient No. 6 the mild paraplegia and retinal hæmorrhages occurred simultaneously but, in patient No. 10, the hemiplegia occurred seven years before her first vitreous hæmorrhage and the association may have been purely coincidental.

3 further patients had cerebrospinal fluid changes without abnormal neurological signs. In patient No. 1 the mildly "paretic" colloidal gold curve suggested a recent increase of protein content. Patient No. 2 had three lumbar punctures at intervals of approximately two years, during which time he had severe, recurrent vitreous hæmorrhages. On each occasion there was a moderate increase of cellular and protein content and, on the last, a grossly abnormal "paretic" Lange curve. Culture was repeatedly sterile. Patient No. 16 had three lumbar punctures in five weeks, and showed a progressive fall of protein from 100 mg. to 30 mg. per cent while retinal hæmorrhages were being absorbed.

Thus, at least 6 out of 17 cases in the present series showed evidence of neurological disturbance bearing a close temporal relationship to active retinal vasculitis. A possible genetic link is suggested by the occurrence of retinal vasculitis in the sister of a young man who attended the Bristol

XUM

Eye Hospital with three attacks of retrobulbar neuritis leading to optic atrophy. (The sister is not included in this series but both siblings were examined by Dr. A. M. G. Campbell.) It is the view of the writer that, in some patients afflicted with retinal vasculitis, similar non-specific inflammatory lesions probably occur in the vessels of the parenchyma and meningeal coverings of the brain and spinal cord. Perhaps it may be said, in conclusion, that the discovery by Ballantyne and Michaelson (1937) and by Verhoeff and Simpson (1940), of lesions affecting the central retinal vein within the optic nerve bridges the imaginary gap between the retina and the remainder of the central nervous system and reminds us that in fact there exists, between the two, anatomical and functional continuity.

Summary

The clinical and laboratory findings in 17 patients with retinal vasculitis and recurrent intra-ocular hæmorrhages (Eales' disease) are reported. 7 patients showed evidence of neurological disorder for which no overt cause could be found in all but one. A high degree of cutaneous sensitivity to old tuberculin was demonstrated in 10 patients out of 15 tested. 6 out of 12 brucellin tests made were positive and 1 patient possibly had chronic brucellosis. The significance of these findings is discussed.

Only 29 per cent of this series had unimpaired sight when last examined, whatever treatment was given. Residual impairment of sight was found to be caused mainly by unabsorbed vitreous hæmorrhages and retinitis proliferans, particularly when they interfered with macular vision.

The ætiology and neurological complications of retinal vasculitis are discussed and the relevant literature is reviewed. It is believed that retinal vasculitis, having several features in common with erythema nodosum, is a non-specific reaction to various infective and possibly toxic agents, and it is suggested that similar inflammatory vascular lesions also occur in the central nervous system in a proportion of cases.

I wish to thank the Consultant Ophthalmic Surgeons of the Bristol Eye Hospital for permission to investigate patients under their care and publish details of them. I am particularly grateful to Dr. A. M. G. Campbell, who prompted this inquiry and has given constant encouragement and advice, and to Professor C. B. Perry for his helpful criticism. This paper contains the substance of a communication presented at a meeting of the Association of British Neurologists, at Bristol, on April 12, 1958.

REFERENCES

Axenfeld, T. (1920) *Ber. dtsch. Ophth. Ces.*, **42**, 298.

—— and Stock, W. (1911) *Klin. Mbl. Augenheilk.*, **49** (i), 28.

Bahr, G. von (1938) *Acta Ophthal., Kbh.*, **16**, 101.

Ballantyne, A. J., and Michaelson, I. C. (1937) *Brit. J. Ophthal.*, **21**, 22.

——, —— (1947) *Trans. Ophthal. Soc. U.K.*, **67**, 59.

BARRETT, G. M., and RICKARDS, A. G. (1953) *Quart. J. med.*, **22** (n.s.), 23.
BECK, A., HUTCHINGS, M. W., MAKEY, A. R., and TUCK, I. M. (1955) *Lancet*, **1**, 535.
BENDER, M. B. (1935) *Amer. J. Ophthal.*, **18**, 148.
BIRNBAUM, W., PRINZMETAL, M., and CONNOR, C. L., (1934) *Arch. intern. Med.*, **53**, 410.
DALRYMPLE-CHAMPNEYS, SIR WELDON (1960) "Brucella Infection and Undulant Fever in Man," London, p. 107.
DAVIS, A. E. (1912) *Trans. Amer. Ophthal. Soc.*, **13**, 235.
EALES, H. (1880) *Bgham med. Rev.*, **9**, 262.
—— (1882) *Ophthal. Rev.*, **1**, 41.
FINNOFF, W. C. (1921) *Trans. Amer. Ophthal. Soc.*, **19**, 238.
FOGGITT, K. D. (1954) *Brit. J. Ophthal.*, **38**, 273.
FRIEDENWALD, J. S. (1940) *Arch. Ophthal. N.Y.*, **24**, 652.
GILBERT, W. (1935) *Klin. Mbl. Augenheilk.*, **94**, 335.
GREENFIELD, J. G. (1958) "Neuropathology." London, p. 448.
HAARR, M. (1948) *Acta Ophthal., Kbh.*, **26**, 41.
HARRIS, H. J. (1950) "Brucellosis (Undulant Fever)—Clinical and Subclinical." 2nd ed., New York, p. 343.
HUTCHINSON, H. P. (1932) *Brit. J. Ophthal.*, **16**, 513.
JEFFERSON, M. and CLOAKE, P. C. P. (1952) *Brit. J. Ophthal.*, **36**, 143.
JONES, B. R. (1954) *Trans. Ophthal. Soc. U.K.*, **74**, 119.
KNAPP, P. (1935) *Klin. Mbl. Augenheilk.*, **94**, 748.
LEVER, W. F. (1954) "Histopathology of the Skin." 2nd ed., Philadelphia, p. 95.
MARCHESANI, O. (1935) *Arch. Augenheilk.*, **109**, 124.
—— and STAUDER, K. H. (1935) *Arch. Augenheilk.*, **109**, 281.
MILLER, H. G. (1958) Personal Communication.
O'MALLEY, C. L. C. (1944) *Trans. Ophthal. Soc. U.K.*, **64**, 261.
PERRY, C. B. (1944) *Brit. med. J.*, **2**, 843.
ROTNES, P. L. (1936) *Acta derm.-venereol., Stockh.*, **17** (suppl. III), p. 117.
RUCKER, C. W. (1945) *J. Amer. med. Ass.*, **127**, 970.
SAFÁR, K. (1928) *V. Graefes, Arch. Ophthal.*, **119**, 624.
SCHMID, A. E. (1945) *Ophthalmologica, Basel*, **110**, 259.
SILFVERSKIÖLD, B. P. (1947) *Arch. Neurol. Psychiat., Chicago*, **57**, 351.
SINCLAIR, H. M. (1956) *Lancet*, **2**, 1215.
TERRY, R. (1949) *Brit. med. J.*, **1**, 657.
VERHOEFF, F. H. and SIMPSON, G. V. (1940) *Arch. Ophthal. N.Y.*, **24**, 645.
VEIRS, E. R. (1948) *Amer. J. Ophthal.*, **31**, 168.
WYBAR, K. C. (1952) *Proc. R. Soc. Med.*, **45**, 315.

XUM

THE PLACE OF OPHTHALMODYNAMOMETRY IN THE INVESTIGATION OF CEREBROVASCULAR DISEASE

BY

L. A. LIVERSEDGE AND VERNON H. SMITH

(From the Manchester Royal Infirmary and Manchester Royal Eye Hospital)

WITH the advance of technical virtuosity in arterial surgery the early diagnosis of the precise site of an occlusive episode in the vascular supply to the brain has become a matter of some importance, and Rob (1953 and 1960) has further showed the importance of surgery in the pre-thrombotic stage of arterial stenosis. The modes of presentation of stenosis and thrombosis of the internal carotid are notably confusing and comprise a quite extraordinary spectrum of clinical patterns ranging from a progressive dementia (Fisher, 1954) or cerebral tumour (Clarke and Harris, 1958) to an apparent central retinal artery thrombosis (Smith and Liversedge—in preparation). Carotid arteriography will reveal the site and degree of affection of the artery but our view is that percutaneous angiography is not without risk to an artery which is already diseased and that this procedure by its local traumatic effects interferes significantly with the task of the surgeon if operation on the stenosed or obliterated artery is advised.

For this reason we have been interested to review the value of ophthalmodynamometry in the diagnosis of cerebro-arterial disorder and because of the varying opinions expressed in the past, we felt it important to approach the problem anew and to establish our own standards of technique and of clinical appraisal.

TECHNICAL CONSIDERATIONS

The technique of ophthalmodynamometry was described by Bailliart (1917) and Magitot (1922) as a means of measuring the pressure in the central retinal artery. However, Duke-Elder (1926) and Adler (1950) pointed out its inaccuracies, showing that what this method really measures is the pressure in the ophthalmic artery. This view is now accepted by most American ophthalmologists (Wagner, 1959).

The technique is still too inaccurate to provide a reliable reading of the blood pressure in the ophthalmic artery *per se*, but may be of value in

comparing the pressures in the two ophthalmic arteries of the same patient, for under these circumstances many of the objections previously adduced no longer apply.

Consequently the technique has been applied to the diagnosis of carotid insufficiency, and its use in this respect has been reported by several workers (Baurmann, 1936; Krayenbühl and Weber, 1944; Milletti, 1950; Drew and Petrohelos, 1951, 1953; Thomas and Petrohelos, 1953; Svien and Hollenhorst, 1956; Heyman, Karp, and Bloor 1957; Wood and Toole, 1957; Spalter, 1959, and Hollenhorst, 1959). Their results show that the fall in pressure which occurs with a block in the common or internal carotid arteries, and proximal to the origin of the ophthalmic artery (Sweet and Bennett, 1948; Sweet, Sarnoff and Bakay, 1950), is transmitted to the latter. Moreover there is experimental evidence (Smith 1961) to show that the pressure in the ophthalmic artery in experimental carotid occulsion is practically the same as that immediately distal to the carotid block.

The Technique of Ophthalmodynamometry

(1) *The Instrument*

The dynamometer in common use is that designed by Bailliart (1917) and described by him in his classical paper. It consists of a spring-loaded piston to which is attached a footpiece (fig. 1, Plate XXIX) which is placed in contact with the sclera. The footpiece is a smooth convex disc, designed in such a way as to slide away from the point of contact unless the piston is held at right angles to the eye. The piston is partly contained within a cylinder, by which the instrument is gripped, and when pressure is applied on the footpiece the piston protrudes from the distal end of the cylinder to a proportionate extent. This part of the piston is callibrated in grammes, and provides a reading of the pressure exerted on the eye. Attached to the cylinder is a brake, by which the movement of the piston within the cylinder can be halted instantly at any pressure stage desired (fig. 2).

(2) *The Preparation of the Patient*

The investigation is performed with the patient lying supine. Recent workers (Smith, Zieper and Cogan, 1959) have shown the results obtained when the examination is performed in this position are more clearly defined than those carried out in the erect posture. The pupils are dilated with homatropine and cocaine, though Spalter (1959) maintains that mydriasis is not necessary in the majority of cases. This may well be true, but an adequate examination of the periphery of the fundus is impossible without a dilated pupil, and it is important that such an examination should be made in all cases, for one case in this series was considered unsuitable for ophthalmodynamometry when a retinal tear was discovered by careful examination of the periphery. It is felt that the avoidance of technical

XUM

complication can only be achieved if this precautionary examination is performed in all cases. Decicaine drops are instilled next and a Schiotz reading taken from both eyes. Apart from the essential information thus obtained, this procedure helps to gain the confidence and co-operation of the patient by its painless nature. The patient must be instructed to keep his eyes closed, apart from the times of examination of the fundus, to prevent corneal drying. The blood pressure is now taken in both arms. If a significant and reproducible difference is present between the pressures from the two sides this may have considerable bearing on the interpretation of the results.

(3) *Contra-indications*

Certain contra-indications may be regarded as absolute, as for example when ophthalmodynamometry would be prejudicial to sight, as in the case of intra-ocular tumours, recent intra-ocular surgery, retinal detachment, or a rise in intra-ocular pressure suggestive of closed angle glaucoma. Others may be classed as relative contra-indications, and amongst these one includes retinal tear without detachments, and intra-ocular inflammation including iritis. In such cases it must be recalled that ophthalmodynamometry, like angiography, is an accessory investigation in the diagnosis of cerebrovascular disease, and that the possible value of the procedure must be balanced against possible complications. In the presence of symptoms of arteriosclerotic retinopathy, or advanced chronic simple glaucoma, a further diminution of retinal blood supply, even of a transient nature, could well produce further permanent damage. To perform ophthalmodynamometry on such a case the indications for the procedure would have to be very strong indeed, and the position explained to the patient after discussion between the ophthalmologist and his medical colleagues.

(4) *The Measurement of the Pressures*

The technique for measuring the ophthalmic artery pressure in the right eye will be described. For measurement of the left eye the directions for right and left are reversed. The patient is instructed to look up at the ceiling, to keep his eyes still, and not to blink. The local anæsthetic instilled for the Schiotz reading should be sufficient for the subsequent procedure. The dynamometer is gripped between the thumb and index finger of the left hand, and after steadying the instrument by placing the little and ring fingers against the patient's temple, the footpiece is placed in contact with the globe opposite the insertion of the lateral rectus muscle (fig. 3). The position of the thumb is important. It should be placed so that it is partly on the brake, which indeed may be slightly depressed, providing that this is not sufficient to cause friction on the piston. Holding the ophthalmoscope in the right hand, and viewing the patient's disc with

the right eye, the pressure on the patient's globe is increased (fig. 4). The following changes are seen:

(1) A transient venous pulsation.
(2) A slight arterial pulsation. This progresses until it becomes:
(3) A collapsing arterial pulsation. This point represents equalization of the diastolic pressure. The brake is applied and a reading taken.
(4) The dynamometer is reapplied to the eye and further pressure exerted. The collapsing pulsation diminishes in amplitude and finally disappears. This point represents the systolic pressure. The brake is applied again and the reading taken. At this moment an observant patient will notice that his vision disappears in the eye under examination.

A few technical points require further mention. The speed at which the measurements are performed must be the same on the two sides. Furthermore, this must not be too rapid, as time must be given for the pressure in the central retinal artery to build up to that of the ophthalmic. However, once the systolic pressure is reached, and the instrument is kept in contact with the eye, maintaining its pressure, the pulsations in the central retinal artery will reappear. This is due to aqueous being extruded from the eye, thus diminishing the cushion between the retinal blood pressure and the dynamometer. Further pressure on the dynamometer is required to obliterate this pulsation.

Subsequent readings, therefore, give a higher result if performed soon after the original measurement, but provided that this is realized there is no harm in such repetition. In the series reported below a rise of 5 grammes in the systolic pressure was seen with each subsequent reading. If, however, there was undue disproportion between the times taken to measure the two sides at the first attempt, it is better to wait for twenty minutes for the aqueous to reform and then repeat the readings *de novo*.

(5) *Complications*

A certain amount of co-operation from the patient is essential, and although some complain afterwards of the efforts of will involved in keeping their eyes still for the half minute or so required, all are agreed that the examination is not painful. Occasionally, a more restless patient may get a small subconjunctival hæmorrhage, but the main danger is corneal drying. It is the more co-operative patient who tends to suffer from this, since having been warned not to blink at an early part of the procedure, he does his best not to do so, aided by the surface anæsthetic previously instilled. Unless he is told to keep his eyes closed whenever possible, drying is very prone to occur in this type of case.

(6) *Assessment of the Results*

It is important to establish that the readings obtained from the dynamometer are purely arbitrary units of extra-ocular pressure, and are not to be

XUM

regarded as accurate measurements of the ophthalmic artery pressure. Some indication of the blood pressure may be reached by adding the intra-ocular pressure to the dynamometer reading, but this is only a very rough approximation. However, in one patient (Case 17) the dynamometer readings from both eyes, although equal, were so low that even when added to the intra-ocular pressure, the combined total was barely half the blood pressure. This case was diagnosed as a bilateral carotid occlusion, and the diagnosis was confirmed by angiography. There exists in the literature some controversy over the end point to be chosen as representing the diastolic pressure. Some workers (Drew and Petrohelos (1951): Heyman, Karp and Bloor (1957): Smith, Zieper and Cogan (1959)) regard the first visible pulsation in the central retinal artery as equivalent to that point, as did the originators of the technique (Bailliart, 1917; Magitot, 1922). However, Svien and Hollenhorst (1956), and Spalter (1959) regard the first collapsing pulsation as the diastolic end point, and the present authors agree with this view. With very high magnification a pulsation—though not collapsing in nature—is visible under normal conditions, and it is felt that the moment of maximal pulsation, when the vessel is first seen to be collapsing completely, corresponds more closely to the accepted end point for the diastolic pressure when taking the blood pressure with a sphygmomanometer round the arm.

Concerning the difference between the readings from the two eyes that should be considered as significant, there is perhaps less disagreement. The opinion of Thomas and Petrohelos (1953) adopted by Svien and Hollenhorst (1956) and confirmed by Spalter (1959) was that a difference of more than 15 per cent in the systolic and 10 per cent in the diastolic readings should be considered significant, and these figures, broadly speaking, have been accepted and confirmed by the present authors.

There are, however, certain reservations. The literature on opthalmodynamometry gives the impression that it is a very easy procedure, but this had not been our constant experience. With a good patient, who co-operates well, with clear media and isometropic refraction, any difference of more than 15 per cent in the systolic pressures would certainly be considered significant, provided that the Schiotz and blood pressure readings were practically equal. In fact we have taken a figure of 20 per cent and above as being significant in our cases.

If, however, the patient is anisometropic, or co-operates poorly, or has opacities in the media, we feel that the experimental error is greater, and that a more clear-cut difference is required before it can be considered as significant. Fortunately by far the majority of cases fall into the first group, but as decisions of some gravity may be based on the ophthalmological findings we feel that it should be recognized that the procedure is not always easy, and that considerable judgement may be required in the interpretation of the results.

With regards to the diastolic pressure we find ourselves unable to confirm completely the results of the workers quoted above. In the majority of our cases the diastolic pressures have shown differences proportionate to the systolic when there has been a significant fall on one side. We have, however, noted cases in our control series where there were differences in the diastolic pressures that would be regarded as significant by the authors already quoted, but where the systolic readings were almost equal. Furthermore, we have examined cases where the diastolic readings were similar, but where a significant difference existed between the systolic readings, thus supporting the work of Milletti (1950) and Heyman, Karp and Bloor (1957). Consequently we cannot support the view of Svien and Hollenhorst (1956); Schimek and Beallo (1959) and Smith, Zieper and Cogan (1959) that only diastolic readings should be taken. If this became universal practice we feel that both false negative and positive results would increase, especially in view of the differences of opinion that exist over the diastolic end point. We regard the diastolic pressure as requiring a far greater degree of experience to elicit accurately than the systolic, and we feel that should only one reading be possible, due to particular circumstances, this should be a systolic and not a diastolic reading.

TABLE I.—PATIENTS ON WHOM CAROTID LIGATURE HAD BEEN PERFORMED

Case	*Interval Between Operation and Dynamometry*	*Dynamometry Readings* Right	Left	*% Deficits* Systolic	Diastolic		*Operation*	
*1	18 months	90/40	60/40	33	0	L	Common	Ligature
2	2 months	75/55	120/85	46	35	R	,,	,,
*3	6 years	40/20	110/60	63	66	R	Triple	,,
4	12 months	95/55	60/35	37	36	L	Common	,,
5	18 months	120/80	80/40	33	50	L	,,	,,
6	13 months	115/70	85/55	26	21	L	,,	,,
7	12 months	95/50	155/80	39	37	R	,,	,,
8	3 years	75/50	55/40	27	20	L	,,	,,
9	4 years	100/80	75/40	25	50	L	,,	,,
10	2 days	80/45	135/50	40	10	R	,,	,,
11	1 month	65/50	140/100	55	50	R	,,	,,
			Mean,	38	36			
	2 Cases who had Direct Clip of Aneurysm							
12	2 years	105/70	110/60	5	†			
13	2 years	105/50	130/55	20	9			

(†In Case 12 the systolic reading was higher on the left and the diastolic higher on the right)

These Cases were Examined Through the Kindness of Mr. R. T. Johnson and Mr. J. Potter

(Cases marked with asterisk are discussed in detail in the text)

XUM

TABLE II.—PATIENTS WITH ANGIOGRAPHIC AND/OR OPERATIVE CONFIRMATION OF CAROTID STENOSIS

	Dynamometry Readings		*% Deficits*	
Case	*Right*	*Left*	*Systolic*	*Diastolic*
*14	110	130	16	Not done
15	50	90	44	Not done
16	70/30	130/110	46	73
*17	70/60	70/60	0	0
18	75/55	110/80	32	31
19	55/30	120/70	54	57
20	50/35	110/60	50	41
21	120/70	90/40	25	43
22	145/90	95/75	34	17
*23	135/85	140/65	0	0
*24	135/85	65/45	52	47
25	120/80	80/40	33	50
26	100	70	30	Not done
		Mean deficits,	32	37 (10 readings)

(Cases marked with asterisk are discussed in detail in the text)

TABLE IIIA.—CONTROL CASES ON WHOM ANGIOGRAPHY WAS PERFORMED AND SHOWED NO EVIDENCE OF CAROTID STENOSIS

	Dynamometry Readings		*% Deficits*		
Case	*Right*	*Left*	*Systolic*	*Diastolic*	*Diagnosis*
27	150+	150+	0	Not done	Right middle cerebral occlusion
28	150+	150+	0	Not done	Right posterior cerebral occlusion
29	150+	150+	0	Not done	Brain-stem thrombosis
30	110/90	130/90	16	0	Subarachnoid hæmorrhage
31	150+/70	150+/70	0	0	Hypertension
32	110/80	110/75	0	6	Left middle cerebral occlusion
33	120/80	130/80	8	0	Parasellar meningioma
34	110/70	110/65	0	7	Right middle cerebral occlusion
35	100/60	90/50	11	16	Migraine
*36	140/80	150/90	7	9	Cerebral arteriosclerosis
*37	100/80	120/80	17	0	"Pseudo-tumour"
38	110/75	110/70	0	7	Right glioma
39	90/40	100/40	11	0	?? Multiple sclerosis
40	110/60	120/70	8	14	Left middle cerebral occlusion
41	130/100	130/100	0	0	Right cerebral agioma
42	110/70	110/70	0	0	Left middle cerebral occlusion
43	150+/130	150+/120	0	8	Supra-sellar meningioma

(Cases marked with asterisk are discussed in detail in the text)

TABLE IIIb.—CONTROL CASES ON WHOM ANGIOGRAPHY WAS NOT PERFORMED

Case	Dynamometry Readings		% Deficit		Diagnosis
	Right	Left	Systolic	Diastolic	
44	145/75	145/75	0	0	Essential hypertension
45	100/70	115/75	13	7	Migraine
46	100/45	100/45	0	0	Motor neurone disease
47	135/80	140/80	4	0	Left middle cerebral occlusion
48	125/80	126/80	0	0	Myocardial infarcation
49	95/50	80/40	16	0	(?) Internal carotid aneurysm
50	110/50	100/60	9	(+16)	Vertigo
51	110/55	105/55	5	0	Disseminated sclerosis
52	90/40	100/40	10	0	Disseminated sclerosis
53	110/80	110/80	0	0	G.P.I.
54	150/90	145/90	3	0	Disseminated sclerosis

Because of the doubts expressed regarding the relative dangers of and the precise diagnostic value of this technique, we began our studies with a fresh appraisal of three groups of patients. The first of these consisted of 11 patients (Table I) (referred to us through the kindness of Mr. R. T. Johnson and Mr. J. Potter) on whom carotid ligature had been carried out as part of the treatment of subarachnoid hæmorrhage in cases of cerebral aneurysms. When ophthalmodynamometry was carried out on these patients we did not know the precise nature of the operative manœuvre and indeed in this group were 2 patients (Cases 12 and 13) who, unknown to us, had not had carotid tie but had been subjected to direct clip of their aneurysms. Correlations between the ophthalmodynamometry readings and the type for carotid tie was made at a later stage. The second group (Table II) contained 13 patients presenting with cerebro-vascular symptoms in whom angiography or local operation in the neck revealed significant carotid stenosis. In certain of these cases the ophthalmodynamometry was carried out retrospectively but in others prior to any operative or angiographic exploration. The third group included 32 patients some of whom had presented with cerebral neurological symptoms but the majority of whom could be regarded as controls whose symptoms had no relation to intracerebral pathology. Ophthalmodynamometry was carried out without knowing the exact diagnosis, and so they do represent adequate

XUM

technical controls. In 19 of these angiograms were also performed (Table IIIA) and it will be noted that in 4 cases there was a middle cerebral occlusion demonstrated clearly on angiography. (Table IIIB lists the control cases on whom no angiogram was carried out.)

Discussion of Results

Group I.—We must repeat that the ophthalmodynamometry readings are not regarded as absolute figures of retinal artery pressure, and that the results are expressed as a percentage difference in the ophthalmodynamometry on the right and left sides. Table I shows the percentage difference in systolic and diastolic pressures, and also indicates the site of the ligature which was applied to each of the patients. The difference in systolic pressure ranged from −25 per cent to 63 per cent (mean −38 per cent) and in diastolic from 0 per cent to 66 per cent (mean 36 per cent). These differences in pressures we refer to hereafter as systolic or diastolic deficits. The greatest combined difference was observed in Case 3 where the difference both in systolic and diastolic pressures was in the region of 65 per cent. This patient was originally treated with common carotid artery ligature, but subsequently developed a post-operative aneurysm in his neck, and so it became necessary to apply ligatures to the common, internal and external carotid arteries. In his case, therefore, the retinal artery on the affected side depended for its blood supply on the circle of Willis together with collateral circulation from the terminal branches of the facial and maxillary arteries on the normal side. It is scarcely surprising, therefore, that even six years after the surgical manœuvres there was still this striking difference in the pressures obtained.

At the other end of the scale lies Case 1, who eighteen months after the application of a common carotid tie showed a systolic deficit of 33 per cent, but no diastolic deficit at all. This we feel reinforces our view that the systolic deficit is a more valuable index of internal carotid flow. Cases 12 and 13 are deliberately included in this "surgical" group and only later were discovered to have had no ligature applied to their carotid arteries. It will be noted that Case 12 had a systolic deficit of 5 per cent but the diastolic deficit of 14 per cent was on the opposite side. Case 13 had a 20 per cent systolic deficit. This patient was treated with a direct intracranial clip of an aneurysm. The post-operative angiographic appearances showed that the right internal carotid artery was narrower than the left and that the right anterior cerebral failed to fill from this side. It seems reasonable, therefore, to suggest that the operative procedure may well have affected the right ophthalmic artery to produce this false positive deficit. We feel that the results obtained justify the deduction that the information obtained from careful ophthalmodynamometry reflects the diminution in carotid flow.

Group II.—The patients in this group all presented as examples of inter-

mittent or progressive affection of cerebral function sometimes with associated optic disorder, and, in short, with the types of clinical picture which we now know to be suggestive of internal carotid artery occlusion. It should be stressed once more that the ophthalmodynamometry was carried out (by V. S.) without prior knowledge of the diagnosis and care was taken to mingle control cases with this particular series. The average systolic deficit was −32 per cent and the diastolic deficit was −37 per cent —figures similar with those noted in Group I. There was a fairly wide variation, however, in these figures and we feel that 4 of these cases call for special comment.

Case 14 was known to have a definite internal carotid artery occlusion and the angiograms (figs. 5 and 6) illustrate this. It will be seen in these illustrations that there is an abundant filling of the carotid siphon via a remarkable collateral circulation through the external carotid, maxillary, facial and ophthalmic arteries. The systolic deficit was only −15 per cent in this case and at this time we were not carrying out diastolic pressure, so we do not know the precise figure. This figure of −15 per cent is slightly below our critical level and it seems that the period of twenty-one months which had elapsed between the actual occlusion and the subsequent measurement of pressures had permitted this extensive collateral circulation to develop. It only remains to add that this patient two-and-a-half years after this occlusion was in good health and showed no additional neurological abnormality.

Case 17.—The point of interest in this case is that there was no systolic and no diastolic deficit. This patient, a man, developed at the age of 53 an attack of blurring of vision in the left eye associated with numbness and weakness of the right arm. This condition improved during the subsequent two weeks and he was admitted to the Manchester Royal Infirmary on 28.6.57 about one month after the onset of symptoms. At that time the only detectable abnormality was a slight degree of nominal dysphasia. Examination of the cerebrospinal fluid and electroencephalogram were normal. Left common carotid angiogram (15.7.57) showed a narrowing of the internal carotid artery about 1 cm above the bifurcation and extending for a distance of 0·75 cm. This narrowing was felt to be due to an atheromatous plaque. The patient continued to improve and was accordingly discharged without further treatment on 19.7.57. On 29.8.57 he suddenly developed weakness of the right arm and leg and a severe degree of dysphasia. On admission to hospital on 5.9.57 he had definite right pyramidal signs with an obvious dysphasia, dyslexia and dysgraphia. He again improved but had an attack of blurring of his left vision on 23.9.57. This cleared within one hour and although operative treatment (either disobliteration or arterial graft) was offered to him, he declined because of continued improvement. He then proceeded moderately well until March 1959 when his work began to suffer because of his difficulty in thinking and in concentrating. In the following month he had a series of attacks of blurring this time of his right vision, and these symptoms continued to trouble him during the next three to four months. He was readmitted to hospital on 13.10.59 when examination showed he still had the partial right sided pyramidal signs with the dysphasia, dysgraphia and dyscalculia.

Bilateral carotid angiography was carried out on this occasion revealing a complete left carotid occlusion and a severe degree of stenosis on the right side. Blood pressure was 160/90 in both arms and ophthalmodynamometry readings 4.11.59 were right eye 70/60, left eye 70/60. The tomometry (Schiotz) 17 in each eye. It will be seen that in this case there was no systolic or diastolic deficit. If, however, one adds the tomometry

XUM

reading to the systolic ophthalmodynamometer reading the figure obtained is just over 50 per cent of the systemic blood pressure, whereas in the normal course of events this combined figure amounts to 80 per cent or higher of the systolic pressure. Three days after angiography this patient's condition deteriorated very rapidly. Bilateral carotid arterial disobliteration was carried out (Mr. K. Bloor). Both the carotid arteries were found to be occluded and unfortunately no satisfactory backflow could be obtained. Post-operative ophthalmodynamometry showed no improvement in the previous figures The patient continued to be no worse than he was prior to operation and, in fact, made a slight improvement. Three points emerge from this interesting story. The first is the illustration of the fact that combined tomometry and ophthalmodynamometry will give a crude measure of the real pressure in the ophthalmic artery. Secondly, angiography may indeed be followed by aggravation of the stenosis, for although it may be argued that this patient would have deteriorated in any case the final occlusive episodes in the left and then the right carotid artery followed very closely upon carotid arteriography. The third point of interest is that a patient, though considerably handicapped, can continue to survive even after bilateral carotid thrombosis as was demonstrated by Fisher (1954), Clarke and Harrison (1956) and Groch *et al.* (1960). Our series contained another patient who also developed bilateral carotid occlusion and yet survived.

Case 23.—We feel this case calls for comment because it illustrates the limitations of the technique and shows that normal ophthalmodynamometry does not necessarily mean that there is no carotid abnormality.

A male, aged 57, on 2.2.60 complained of sudden difficulty in picking up objects with his right hand. This complaint continued for the next forty-eight hours, but then improved. Four days later he had an attack of unconsciousness and after recovering consciousness had developed a complete right hemiparesis which, however, cleared completely within the space of three to four hours. On 15.2.60 he was referred to Mr. John Potter who detected some defects of fine movements in the right hand and a degree of astereogmosis but no other significant neurological abnormality. Clinical re-examination on 2.3.60, however, showed that the reflexes in the right arm and leg were a little brisker than those on the left side, and that his right plantar response was equivocal. In addition to this he showed a most interesting dysgraphia which is

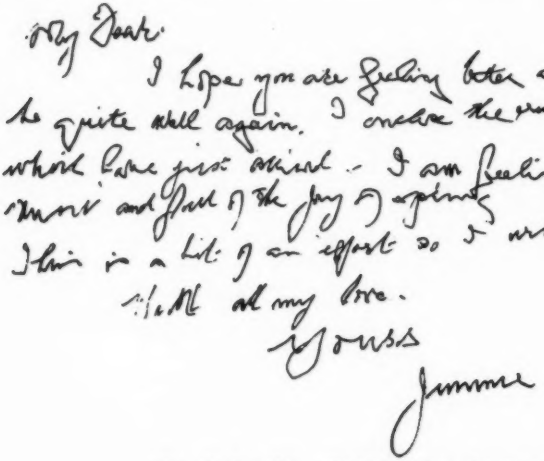


FIG. 7 (*Case* 23).—Writing before the operation.

illustrated in fig. 7. Dynamometry performed at that time showed that there was a systolic deficit but the readings on the right side were 130/65 and on the left 115/65—thus giving a deficit of only 11 per cent in the systolic pressures. We do not regard this figure as being significant for it is not outside the limits of experimental error in our series. Because of the history, however, left carotid angiography was performed and showed a definite stenosis in the left internal carotid artery as shown in fig. 8. Disobliteration was carried out (Mr. Kenneth Bloor) and an atheromatous plaque was clearly visible at operation. At operation direct measurement of the intra-arterial pressures above and below this plaque, using intra-arterial needles and a strain gauge, showed that the intra-arterial pressures both above and below the plaque were identical at 130 mm. It seemed, therefore, that the normal reading on ophthalmodynamometry reflected quite correctly the state of affairs in the carotid arteries. Following disobliteration this patient improved symptomatically and showed an interesting amelioration in his writing (fig. 9). One must conclude, therefore, that in spite of normal

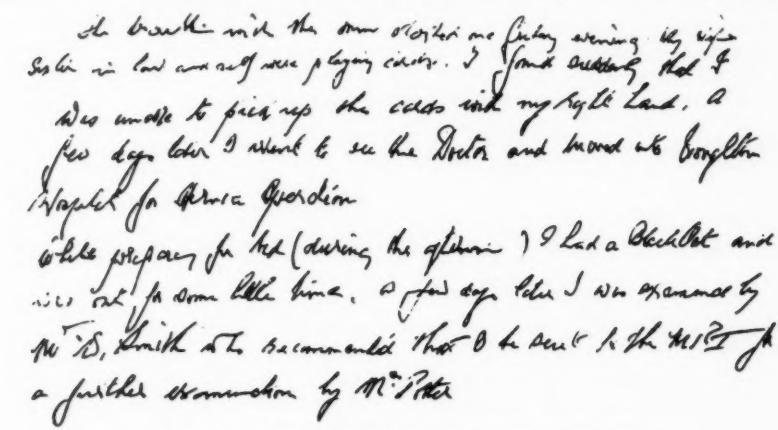


FIG. 9 (*Case* 23).—Writing on the day after operation.

pressure readings there was a definite impedance of the total blood flow with resultant ischæmia and subsequent neurological deficit. As stated above this case shows that ophthalmodynamometry cannot demonstrate the existence of minor degrees of carotid stenosis. It is perhaps significant, however, that in this case carotid angiography was not followed by an increase in symptomatology and it is possible that if ophthalmodynamometry is normal one may regard angiography as a relatively safe procedure even in cases where there is arterial abnormality.

Case 24.—A male, aged 44, in August 1959, developed numbness and jerking of the right leg which lasted only thirty seconds. In September 1959 his right hand became numb and tingling for a space of one minute and after this his right face was affected for a few seconds. Subsequently he had two or three similar attacks affecting either his leg, hand, or face, or occasionally all three, in each week. The duration of each attack was rarely more than one minute. On 4.3.60 he was admitted to hospital because of the continuation of these symptoms and clinical examination at that time revealed:

Blood pressure 200/125.

Tendons reflexes brisker on the right side than the left.

Both plantar responses flexor.

XUM

There was undoubted diminution in the volume of the carotid pulse on the left side and this was considered to be significant by certain observers though not by others. Ophthalmodynamometry on 11.3.60 revealed pressures on the right side 135/85, left 65/45, a systolic deficit of 50 per cent and a diastolic deficit of just under 50 per cent. Operation was being considered as a result of these findings but before it could actually be carried out the patient suddenly developed complete aphasia with complete right hemiplegia on 21.3.60. Disobliteration of the left carotid artery was carried out within four hours of this catastrophe and Mr. K. Bloor's operation note reads: "The internal carotid did not pulsate and there was a complete block at the bifurcation, not extending into the external carotid. An incision about 2 cm long was made into the commencement of the internal carotid and the bifurcation. During disobliteration back bleeding from the internal carotid artery occurred immediately. I received the impression that the artery had only recently thrombosed completely, there was some recent clot completely blocking the internal carotid at the atheromatous plaque and there was no consecutive clot in the internal carotid artery." Following disobliteration hemiparesis cleared rapidly, though on 25.4.60 there was still some residual disability in the arm. Unfortunately he continued to be severely dysphasic and one cannot yet predict the degree of recovery to be expected in his speech. It is felt that this patient might well have been spared this cerebrovascular catastrophe if operation had been undertaken as soon as the diagnosis was established. We believe, in fact, that in such cases, where progressive stenosis is heralded by recurrent cerebrovascular attacks, early disobliteration is advisable.

Group III (*a and b*).—These 28 patient comprised (*a*) 17 patients who exhibited symptoms of intracranial pathology for which angiography was to be performed and (*b*) 11 others on whom angiography was not performed. It will be seen that in the majority of cases the systolic and diastolic deficits were less than 10 per cent but that figures up to 17 per cent systolic deficit were recorded—this last in a patient who had a perfectly normal angiogram (Case 37). We feel that Cases 27, 32, 34 and 40 are of special interest, for these patients presented with vascular hemiparetic pictures very similar to those seen in certain types of internal carotid artery affection. Dynamometry proved to be within the normal range and the carotid angiography revealed that the site of affection was in the middle cerebral artery only. Case 47 also had normal dynamometry, but angiography was not performed because of the picture of diffuse arteriosclerosis presented by this patient, hence the diagnosis of a middle cerebral occlusion was not absolutely proven, and it is possible, though unlikely, that this patient had some affection of the internal carotid. It seems that ophthalmodynamometry may prove a useful means of differentiating between the internal carotid and middle cerebral occlusions but it must be admitted that falsely negative results *may* have occurred in this particular group on whom angiography was not performed.

Conclusions

As a result of our investigations we feel that certain points may justifiably be made about the real value of ophthalmodynamometry as practised in the way described.

A. *Limitations of the Technique*

(1) It does not give an absolute indication of early stenosis and false negative results may be obtained.

(2) If a positive result is obtained one still cannot deduce the precise site of obstruction in the carotid artery for the dynamometry merely indicates the presence of a lesion between the carotid bifurcation and the origin of the ophthalmic artery.

(3) False positive results may occur. We have encountered one case in the "surgical" group (Case 13) and other one example in a patient suffering from diffuse obliterative arterial disease. In such cases stenosis of the ophthalmic artery or of the retinal artery may be the cause.

B. *Practical Values*

(1) The technique provides useful and reasonably reliable information about the relative pressures in the two internal carotid arteries and so may indicate the presence or absence of a stenosing lesion.

(2) It does help to differentiate between occlusions of the middle cerebral and of the internal carotid arteries.

(3) It can also help to differentiate between the progressive type of carotid occlusion (Clarke and Harris, 1958), and a cerebral tumour.

(4) If a positive result is obtained one may decide to dispense with percutaneous angiography and proceed to immediate operation on the affected artery with a view to disobliteration. The importance of this point lies in the fact that percutaneous angiography may actually precipitate further thrombosis and in any case renders the operative field more difficult for the surgeon.

(5) A normal dynamometry seems to indicate relative safety of percutaneous angiography.

The medical patients referred to in this paper were referred through the kindness of Dr. F. R. Ferguson and Dr. G. E. Smyth, to whom we are further indebted for their interest in this work.

REFERENCES

ADLER, F. H. (1950) "Physiology of the Eye: Clinical Application." St. Louis. p. 246.
BAILLIART, P. (1917) *Ann. Oculist. Paris.*, **154,** 257.
BAURMANN, M. (1936) *Ber. dtsch. ophthal. Ges.*, **51,** 228.
CLARKE, E., and HARRISON, C. V. (1956) *Neurology*, **6,** 705.
—— and HARRIS, P. (1958) *Lancet*, i, 1883.
DREW, A. L. and PETROHELOS, M. A. (1951) *Univ. Mich. med. Bull.* **17,** 282.
——, —— (1953) *J. Neurosurg.* **10,** 74.
DUKE-ELDER, W. S. (1926) *Brit. J. Ophthal.*, **10,** 513.
FISHER, M. (1954) *A.M.A. Arch. Neurol. Pschiat.*, **72,** 187.

XUM

GROCH, S. N., HURWITZ, L. J. and MCDOWELL, F. (1960) *Arch. Neurol.*, **2**, 130.
HEYMAN, A., KARP, H. R., and BLOOR, B. M. (1957) *Neurology*, **7**, 97.
HOLLENHORST, R. W. (1959) *Amer. J. Ophthal.*, **47**, 753.
KRAYENBÜHL, H., and WEBER, G. (1944) *Helv. med. Acta.*, **11**, 289.
MAGITOT, A. P. (1922) *Amer. J. Ophthal.*, **5**, 777.
MILLETTI, M. (1950) *Acta Neurochir.*, **1**, 196.
ROB, C. G. (1953) *Proc. R. Soc. Med.*, **46**, 121.
—— (1960) *Proc. R. Soc. Med.*, **53**, 38.
SCHIMEK, R. A. and BEALLO, A. (1959) *Amer. J. Ophthal.*, **48** (3) Part 2, p 220.
SMITH, J. L., ZIEPER, I. H., and COGAN, D. G. (1959) *J. Amer. Med. Ass.* **170**, 1403.
SMITH, V., and LIVERSEDGE, L. A. (1960) In preparation.
SMITH, V. H. (1961) *Brit. J. Ophthal.* **45**, i.
SPALTER, H. F. (1959) *Amer. J. Ophthal.*, **47**, 453.
SVIEN, H. J., and HOLLENHORST, R. W. (1956) *Proc. Mayo Clin.*, **31**, 684.
SWEET, W. H., and BENNETT, H. S. (1948) *J. Neurosurg.* **5**, 178.
—— SARNOFF, S. J., and BAKAY, L. (1950) *Surg. Gyne. Obst.*, **90**, 327.
THOMAS, M. H., and PETROHELOS, M. A. (1953) *Amer. J. Ophthal.*, **36**, 335.
VAN ALLAN, M. W., BLODI, F. C., and BRINTNALL, E. S. (1958) *J. Neurosurg.*, **15**, 19.
WAGENER, H. P. (1959) *Amer. J. Med. Sci.*, **238**, 211.
WOOD, F. A., and TOOLE J. F. (1957) *J. Amer. med. Ass.*, **165**, 1264.

FIG. 1.—Standard Baillart dynamometer showing convex foot-piece and position of brake when not applied.

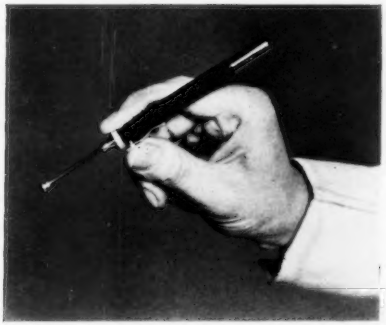


FIG. 2.—Shows standard dynamometer with the brake applied, when the dynamometer was exerting the pressure of 70 grammes.

FIG. 3.—Shows position of dynamometer when applied to the patient's eye.

To illustrate article by L. A. Liversedge and Vernon H. Smith.

XUM

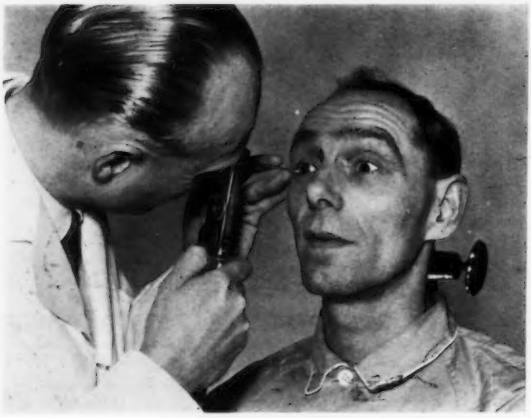


FIG. 4.—Shows relative position of observer and dynamometer. Normally this procedure is carried out with the patient supine.

FIG. 5 (*Case* 14).—Complete occlusion of internal carotid artery at the bifurcation of the common carotid.

To illustrate article by L. A. Liversedge and Vernon H. Smith.

XUM

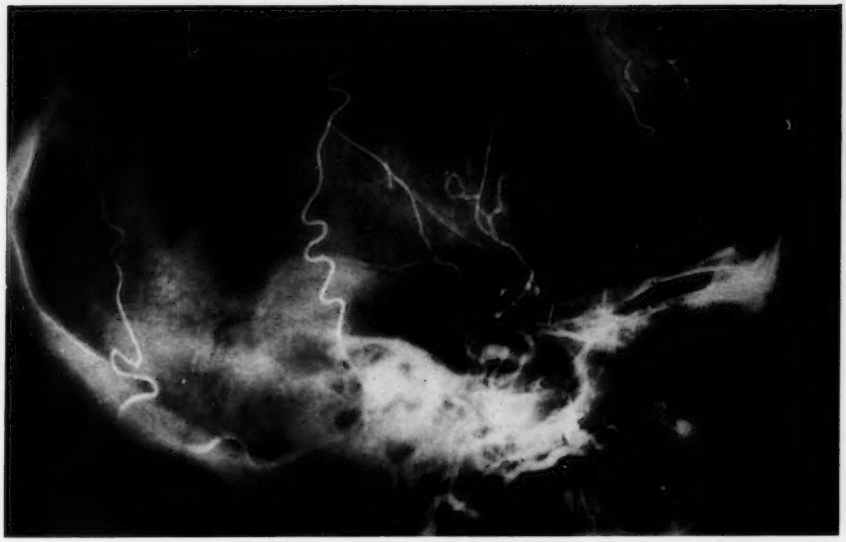


FIG. 6 (*Case* 14).—More detailed view of the collateral circulation through maxillary and ophthalmic arteries filling the carotid siphon.

FIG. 8 (*Case* 23).—Pronounced stenosis at the origin of the internal carotid artery.

To illustrate article by L. A. Liversedge and Vernon H. Smith.

XUM

THE PRIMARY SPINO-CEREBELLAR ATROPHIES AND THEIR ASSOCIATED DEFECTS, WITH A STUDY OF THE FOOT DEFORMITY

BY

J. H. TYRER AND J. M. SUTHERLAND

(From the Medical Professorial Unit of Queensland University, Brisbane Hospital, Brisbane, Australia)

A CLASSIFICATION of the primary spino-cerebellar atrophies based on pathological evidence has recently been published, emphasizing that members of this group of diseases form, as it were, an unbroken chain linked by borderline and transitional cases (Greenfield, 1954; Greenfield *et al.* 1958). Other authors likewise have regarded the boundaries separating various types of spino-cerebellar atrophy as ill-defined or non-existent, including Jendrassik (1902), Raymond (1905), Spillane (1940), Brain (1947), Matthews (1950), Brown (1955), Chandler and Bebin (1956), Poser, Dewulf and van Bogaert (1957) and Fitzgerald and Hyland (1958). Nevertheless Malamud and Cohen (1958) stated that "cases continue to present themselves that are impossible to fit into any scheme."

The protocols of 40 patients in 21 pedigrees are shown in Table I. The series illustrates some rare neurological combinations and some unusual associated defects. In addition, analysis is made of some suggested mechanisms for the foot deformity in Friedreich's ataxia.

STUDIES OF THE FOOT DEFORMITY IN FRIEDREICH'S ATAXIA

Three patients with Friedreich's ataxia were selected (Cases VIII (2), XII (1) and XII (2)), each of whom showed bilateral pes equinus (or equinovarus), pes cavus and slightly clawed toes. In each foot these three deformities were all readily and simultaneously correctable by upward pressure on the first metatarsophalangeal joint with an observer's finger. Case XII (2) appeared to have in addition considerable wasting of the small muscles of the soles of the feet, which contributed to the appearance of pes cavus clinically. The mobile or reversible foot deformities in these patients were deemed suitable for the study of early pes cavus in Friedreich's ataxia.

In each of the six feet with the reversible deformities the following observations were made:

(1) There was no obvious contracture of the soft tissues in the sole of the foot (muscles or plantar fascia), and when the pes cavus was corrected these structures were not unduly taut.

(2) There was no spasticity of muscles in the legs or feet.

(3) If the patient tried to elevate the forefoot voluntarily, considerable difficulty was experienced. The toes usually clawed more markedly, rising further on the tops of the heads of the metatarsal bones and making it mechanically more difficult to elevate the forefoot even when the elevators of the forefoot appeared to be contracting normally. Only one of these three patients was sometimes able to elevate the forefoot voluntarily, after considerable practice, by concentrating attention on unclawing the toes at the same time as trying to elevate the forefoot. Muscle incoordination thus seemed a factor in relation to the difficulty in elevating the forefoot voluntarily.

(4) The first metatarsal bone was firmly grasped between an observer's thumb and forefinger and held fixed in relation to the subject's calcaneum, i.e. the degree of pes cavus was held constant. The observer's other hand was used to hyperextend and hyperflex the toes, but these movements did not alter the degree of pes cavus, i.e. clawing of the toes did not appear to force the forefoot downwards and so produce pes cavus.

(5) With the patient lying so that the lateral surface of the relaxed foot to be investigated was resting on a horizontal smooth board, the foot deformity was corrected by upward pressure on the first metatarsophalangeal joint. The corrected foot position was maintained by a block of wood, with a weight of 10 kg. resting on it to increase the frictional force between the block and the board on which the foot rested (fig. 8, A and B, Plate XXXV). The knee, flexed to 90 degrees, was firmly fixed in one position by slings. Minimal faradic stimulation over the motor points of the various muscles of the leg was then carried out, using a small, moist saline pad 1 cm. in diameter as stimulating electrode and an indifferent plate electrode approximately 5 cm. by 4 cm. on the contralateral thigh. Weak stimulation either of the tibialis posterior or peroneus longus muscle caused drawing down of the forefoot with fair simulation of the relaxed, uncorrected foot deformity (fig. 8, C, D, E and F). Stronger stimulation of the tibialis posterior or peroneus longus muscle caused in addition inversion or eversion of the foot respectively. It was not found possible to reproduce the foot deformity by stimulation of other muscles of the leg or foot.

In these three patients there was at the most no more than slight weakness of voluntary power affecting any of the following muscles: tibialis anterior, tibialis posterior, peroneus longus, extensors of the toes; there was certainly no gross disparity of voluntary motor power between any of them. These muscles were each tested repeatedly by two neurologists and two physiotherapists according to the method of Kendall and Kendall

(1949). The difference of voluntary muscle power between them was so slight that the various observers recorded slightly different opinions.

It seemed that the pes cavus might be due to a preponderance over other muscles of either tibialis posterior, peroneus longus or both. The former was probably the more important as the resting, relaxed feet frequently tended to inversion, but not eversion. Muscle imbalance due to a difference of voluntary power seemed unlikely. Muscle imbalance due to other factors, such as defective cerebellar co-ordination, however, seemed possible.

Faradic stimulation indicated that the action of the lumbricals and interossei in the feet was almost within normal limits, certainly not as weak as the ready clawing of the toes on voluntary effort to lift the forefoot had suggested. Muscle imbalance due to cerebellar dysfunction was again a possibility.

Discussion

The series illustrates typical as well as abortive and transitional forms of primary spino-cerebellar atrophy and supports the contention that these clinical syndromes are but different expressions of the same, genetically determined, degenerative process.

Cases I (1) and (2) and Case II (1) represent a rudimentary type, showing familial pes cavus and claw toes without clinically detectable neurological abnormality apart from the muscular contractures and atrophy related to the foot deformity itself. This type is frequently designated "idiopathic pes cavus and claw toes" by orthopædic surgeons (Wiles, 1955). Lake (1935) noted its occasional familial incidence and suggested an "inborn neuromuscular defect." Spillane (1940) mentioned "isolated familial pes cavus." Though not usually linked with the primary spino-cerebellar atrophies it may be a related abortive form. The occurrence of pes cavus without other neurological abnormality in the sister of X (1) and in the mother of XI (1) is consistent with this view. (Both X (1) and XI (1) had Friedreich's ataxia.)

Case III (3) was regarded as an example of the Roussy-Lévy syndrome (Roussy and Lévy, 1926, 1932) in that there was familial onset of pes cavus and difficulty in walking in childhood; the disease had not progressed over a period of about thirty years; examination of the patient revealed absent knee and ankle jerks and there was no detectable muscle wasting. Case III (2) is probably an instance of the Roussy-Lévy syndrome in that no sign of progress of the disease was detected during the previous three years, the clinical features otherwise being as in III (3). On the other hand Case III (1) showed in addition muscle wasting of the left calf and progression of the disability during the three years' observation period. On these grounds he was regarded as an example of Charcot-Marie-Tooth disease. Similarly we regarded Case IV (1) as an example of Charcot-Marie-Tooth

XUM

disease since the weakness of his ankle movements was sufficiently severe to suggest that his "slender" calves were indeed wasted. The difficulty in deciding clinically as to the presence or absence of muscle wasting, when this is not conspicuous, appears to have been noted by others. Thus in the literature one finds: "La gracilité du tiers inférieur de la jambe, est très notable" (Roussy and Lévy, 1932), without comment regarding actual muscle wasting; and "The calf muscles are thin but do not show any actual atrophy" (Spillane, 1940). Symonds and Shaw (1926) regarded the Roussy-Lévy syndrome as a "forme fruste" of peroneal muscular atrophy. Spillane (1940) considered that the syndrome of Roussy and Lévy is worthy of recognition and "represents a sub-group of the heredofamilial degenerations of the spinal cord and cerebellum of which Friedreich's disease and the muscular atrophy of Charcot-Marie-Tooth are fully fledged examples." In our view, the Roussy-Lévy syndrome occupies a taxonomic position between familial pes cavus and the Charcot-Marie-Tooth disease and it is noteworthy that instances of the Roussy-Lévy syndrome and Charcot-Marie-Tooth disease occurred in the same pedigree.

Cases IV (2), V (1) and VII (1) were examples of Charcot-Marie-Tooth disease, and we regarded VI (1) as a sporadic instance of this disease with associated diabetes mellitus (*see below*).

The two families reported by Roth (1948) suggest a close genetic relationship between Charcot-Marie-Tooth disease and Friedreich's ataxia. In the first family Charcot-Marie-Tooth disease occurred in one member of the pedigree and abortive Friedreich's ataxia in another; in the second family two members of the pedigree each showed classical features of both Friedreich's ataxia and "peroneal" type of amyotrophy.

Cases VIII (1) and (2), IX (1), X (1), XI (1), XII (1), (2), (3), (4) and (5), XIII (1), XIV (1) and XV (1) were classical forms of Friedreich's ataxia. Cases XII (1) and (2), XIII (1) and XV (1) showed significant muscle wasting which, as Matthews (1950) and Bruce (1954) point out, has frequently been described in Friedreich's ataxia (*see below*).

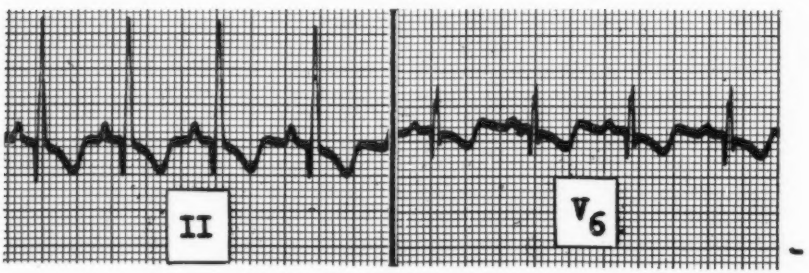


FIG. 5A (*Case XIV* (1)).—Friedreich's ataxia, showing T-wave inversion in the electrocardiogram.

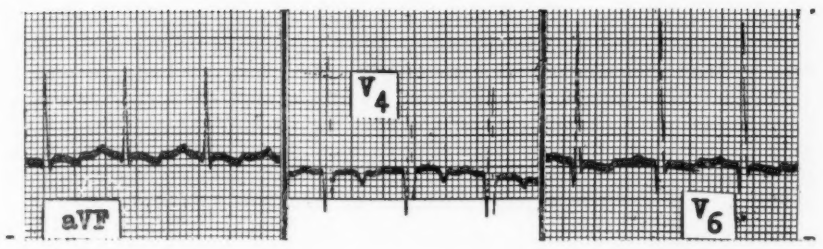


FIG. 5B (*Case XVI* (1)).—Spastic paraplegia, showing T-wave inversion in the electrocardiogram.

Cases XVI (1) and XVII (1), (2) and (3) were examples of spastic paraplegia. Of interest was the occurrence of myoclonus epilepsy in Case XVI (3), who was an aunt of XVI (1). Hunt (1921) noted myoclonus epilepsy in association with Friedreich's ataxia. Greenfield *et al.* (1958) stated that myoclonus epilepsy may combine with spino-cerebellar system degenerations. Thus inclusion of familial spastic paraplegia within the primary spinocerebellar atrophy group appears to make significant the former's association here with myoclonus epilepsy in the same pedigree.

The protein content of the cerebrospinal fluid was slightly elevated in IV (2) and XVII (3) and at the upper limit of normal in XVII (1). In IV (2) autopsy revealed adhesions and formation of calcified plaques in the spinal pia-arachnoid, which might possibly have accounted for the increase of protein in this case.

Using the nomenclature of Greenfield (1954), familial cerebellar ataxia (? Holmes' type) occurred in Cases XVIII (1) and (2), and XIX (1), (2) and (3); Cases XX (1) and XXI (1) were examples of sporadic cerebellar ataxia (? Menzel type of olivo-ponto-cerebellar atrophy).

THE CARDIAC DEFECT

Of the 13 cases of Friedreich's ataxia in 8 pedigrees, electrocardiographic abnormalities occurred in 11 instances. Three of these patients complained of dyspnœa on limited exertion, and Case XIII (1) died suddenly aged 23 years. In the 2 pedigrees showing spastic paraplegia, electrocardiographic abnormalities were found in 3 out of 4 patients with spastic paraplegia, in one relative without neurological defect and in Case XVI (3) who had had myoclonic epilepsy (aunt of Case XVI (1)). In addition an uncle of XVI (1) died suddenly during sleep at the age of 30 years. Four male relatives of Cases XVII (1), (2) and (3) died suddenly before middle age. In these, there was no evidence of neurological disease and no history of rheumatic fever. Case XVI (3) is of interest not only because of spastic paraplegia with cardiac defect in her pedigree but also

XUM

because Harriman and Millar (1955) described intracellular bodies (similar to amyloid Lafora bodies) in the heart of a patient with progressive familial myoclonic epilepsy who came to autopsy.

Cardiac abnormalities in Friedreich's ataxia are well recognized (Greenfield, 1954). In 38 cases reported by Evans and Wright (1942) there were conspicuous electrocardiographic abnormalities in 12 patients and slight abnormalities in 10 others. The underlying myocardial pathology has been discussed by Russell (1946). On the other hand, in familial spastic paraplegia cardiac abnormalities appear to be much less frequent, and indeed are not referred to by Greenfield *et al.* (1958) in relation to this disease. To the cardiac abnormalities affecting two patients with familial spastic paraplegia in one pedigree reported by Sutherland (1957) we have added a further case in another pedigree. In both pedigrees there was evidence of cardiac abnormality in persons free of the spastic paraplegia.

The Foot Deformity

In addition to the 3 cases of familial pes cavus, bilateral pes cavus was encountered in both patients with the Roussy-Lévy syndrome, in all 6 patients with Charcot-Marie-Tooth disease, in 12 of 13 cases with Friedreich's ataxia, in all 4 patients with spastic paraplegia, but in only 1 of the 7 cases of cerebellar ataxia described. The association of pes cavus with one case of cerebellar ataxia of presumed Menzel type supports the relation of this condition to the more spinal forms of spinocerebellar atrophy.

The foot deformity was seen most characteristically and most fully developed in Friedreich's ataxia. At least four features were discernible: (1) pes equinus or pes equinovarus, (2) pes cavus (claw foot, "cave foot"), (3) claw toes, (4) wasting of the small muscles of the sole of the foot. The last contributed to the clinical but not to the radiographic appearance of pes cavus.

In the later irreversible stages of foot deformity, when walking had become impossible, the effects of contractures of muscles and fascia and of the habitual assumption of faulty postures were evident. However, in the cases of mobile or reversible pes cavus here studied in Friedreich's ataxia, the findings were in agreement with Knight (1949) and Wiles (1955) that the high-arched appearance of the foot was due to dropping of the forefoot at the intertarsal and tarsometatarsal joints, which appeared quite lax, rather than to true raising of the longitudinal arch. A number of views have been offered as to the mechanisms causing this type of pes cavus. Lake (1935) cited the view that the dropping of the forefoot is due to weakness or paralysis of the "dorsiflexor group of muscles" and that a similar result may follow division of the tendons of these muscles. In the early cases here studied the voluntary power of the tibialis anterior muscles appeared within normal limits and that of the extensores digitorum only

slightly, if at all, weakened; further, since the toes were hyperextended at the metatarsophalangeal joints, it was difficult to see how weakness of the extensors of the toes could be the primary defect. Knight (1949) quoted Lambrinudi's view that the clawing of the toes arose from paralysis or disturbance of function and balance of the intrinsic muscles of the foot, particularly the lumbrical and interosseous groups, the pes cavus being secondary. Wiles (1955) supported this view and considered that as the toes became clawed and displaced on to the dorsum of the metatarsal heads, they forced the latter downwards to produce pes cavus. In the mobile pes cavus here studied, the joints were lax and hyperextension of the toes seemed to have no significant effect in forcing down the forefoot to produce pes cavus. Knight (1949) cited Bentzon's view that muscle imbalance between peroneus longus and tibialis anterior may produce pes cavus. Makin (1958) suggested that muscle imbalance seemed to be the major factor in the genesis of the foot deformity and that the main deforming factor appeared to be the tibialis posterior muscle, unopposed due to weakness or paralysis of the muscles innervated by the common peroneal nerve.

In relation to the six feet here described with reversible pes cavus, electrical stimulation of either the peroneus longus or tibialis posterior muscles could reproduce pes cavus, being thus consistent with the views either of Bentzon or Makin respectively. More than minimal stimulation of the peroneus longus and tibialis posterior muscles produced some eversion and inversion of the foot respectively in addition. As the resting feet frequently showed slight inversion, but not eversion, it seemed likely that preponderance of the tibialis posterior muscle might be the major factor producing the pes cavus. It was noteworthy that drawing down of the forefoot by stimulation of the tibialis posterior or peroneus longus muscles led to simultaneous clawing of the toes. Conversely pressing the first metatarsophalangeal joint upwards tended to unclaw the toes, and this was observed by Lake (1935) who considered that the clawing of the toes was passive and secondary to the drop of the forefoot. The studies here presented are consistent with this view.

As no significant disparity of voluntary power between the tibialis anterior, tibialis posterior, peroneus longus and extensores digitorum muscles was detected clinically, the muscle imbalance might have been related to a disturbance of cerebellar co-ordination of these muscles. Makin (1958) described normal musculature associated with the foot deformity in 10 out of 43 patients with Friedreich's ataxia where the muscle power was recorded. While weakness of lumbricals and interossei did not appear to be important in the primary cause of the pes cavus, the lack of co-ordinated action of these muscles when the patients tried to elevate the forefoot voluntarily was conspicuous.

Our studies of pes cavus relate only to the reversible early foot deformity

XUM

encountered without spasticity in Friedreich's ataxia. Garland and Astley (1950) noted pes cavus as a constant finding in their cases of hereditary spastic paraplegia. Collier (1899) concluded that spasticity from any cause, if of sufficient duration, tended to cause pes cavus, especially in young people whose skeletal structures are less rigid than in later life. Collier regarded as pertinent the spasticity affecting the extensors of the toes, tibialis posticus and peroneus longus. Pes cavus is also a recognized complication of such conditions as acute anterior poliomyelitis (Knight, 1949) and hereditary hypertrophic "neuritis" (Garland and Astley, 1950). It is possible that the mode of production of pes cavus may vary in different neurological conditions.

Other Associated Defects

Apart from the characteristic foot deformity, kyphoscoliosis, "manus cava" or "intrinsic minus hand" (Makin, 1958) and the myocardial abnormality, numerous other defects have been described, either as manifestations of or in association with the spinocerebellar atrophies. These defects are summarized in Table II.

The statistical significance of many of the defects noted in Table II is difficult to evaluate. Some defects are so frequent as to be almost part of the nosographic description, e.g. pes cavus and myocardial defect in Friedreich's ataxia. Other defects are so rarely associated as to make it difficult to distinguish an uncommon manifestation from an independent defect. Nevertheless some of these defects may at times give clinical support to the diagnosis of primary spinocerebellar atrophy in doubtful sporadic cases. The associated defects may be single or multiple, e.g. in a patient with Friedreich's ataxia described by Stewart (1959) there were associated hypogenitalism, adiposity, choroidal sclerosis and polydactyly, a group of features not far removed from the so-called Laurence-Moon-Biedl syndrome.

In our series kyphoscoliosis occurred in one of the 2 patients with the Roussy-Lévy syndrome, 2 with Charcot-Marie-Tooth disease, 8 with Friedreich's ataxia and in one with spastic paraplegia. Primary optic atrophy was found in 1 patient with Friedreich's ataxia, 3 patients with spastic paraplegia and in 1 relative of a patient with spastic paraplegia. Diplopia occurred in 3 members of a family suffering from cerebellar ataxia; in 2 of these patients extrinsic ocular muscle weakness could be demonstrated clinically, in 1 the pupillary reactions to light were poor. There was 1 patient with *grand mal* epilepsy and 1 with myoclonic epilepsy, these 2 being relatives of a patient with spastic paraplegia. Mental deficiency was encountered in a sibling of a patient with Charcot-Marie-Tooth disease, in 2 patients with Friedreich's ataxia and in 1 patient with spastic paraplegia (a brother of this latter patient also showed mental deficiency). One of the patients with Friedreich's ataxia

TABLE II.—ASSOCIATED DEFECTS WHICH HAVE BEEN DESCRIBED IN RELATION TO THE PRIMARY SPINOCEREBELLAR ATROPHIES (EXCLUDING PES CAVUS, KYPHOSCOLIOSIS AND MYOCARDIAL DEFECT)

Associated defect	*Author(s)*
Primary optic atrophy	Holmes, 1910; André-van Leeuwen, 1948.
Retinitis pigmentosa	Brown, 1955.
Choroidal sclerosis	Stewart, 1959.
Cataract	van Bogaert and Moreau, 1939; Jéquier, 1948.
Ptosis	Gareiso and Pedace, 1948; Jéquier, 1948.
External ocular palsies	Bruce, 1954; Stephens, Hoover and Denst, 1958.
Abnormal pupillary reflexes	Brain, 1947.
Deafness	Brain, 1947.
Deaf-mutism	Matthews, 1950.
Degeneration of brain-stem motor nuclei	van Bogaert, 1951.
Spina bifida occulta	Brain, 1947; Jéquier, 1948.
Sacralized fifth lumbar vertebra	Jéquier, 1948
Syndactyly	van Bogaert and Moreau, 1939.
Polydactyly	Ashby and Tweedy, 1953; Stewart, 1959.
Muscle dystrophy	Greenfield *et al.*, 1957; Stephens *et al.*, 1958.
Epilepsy	Biemond, 1951.
Myoclonic epilepsy	Hunt, 1921; Greenfield *et al.*, 1958.
Mental deficiency	Bell and Carmichael, 1939; Stewart, 1959.
Progressive dementia	Greenfield, 1954; Carter and Sukavajana, 1956.
Paranoia	van Bogaert and Moreau, 1939.
Mongolian idiocy	Degenkolb, 1906.
Diabetes mellitus	Schlezinger and Goldstein, 1940; Biemond, 1951; Ashby and Tweedy, 1953.
Cryptorchidism	Jéquier, 1948.
Infantilism	Brain, 1947; Bruce, 1954.
Hypogenitalism and obesity	Stewart, 1959,
Habitual hyperthermia	Stewart, 1959.

manifested paranoid trends. Idiocy and Mongolian imbecility occurred in 2 nieces of 3 siblings suffering from spastic paraplegia.

We have not found reference to hare-lip and cleft palate or to colour blindness as associated defects, but the former occurred in I (1) and the latter in XVI (3); these associations may be coincidental.

The occurrence of ichthyosis in a patient suffering from Charcot-Marie-Tooth disease (VII (1)) is of interest in view of the reported association of ichthyosis with mental defect and tetraplegia (Sjögren and Larsson, 1957) and with Refsum's syndrome (Fleming, 1957; Ashenhurst, Millar and Milliken, 1958).

The occurrence of diabetes mellitus in association with Friedreich's ataxia has been recognized by several authors and its occurrence in VI (1) appears significant. The obvious condition to be differentiated is diabetic amyotrophy. However, for the following reasons VI (1) was regarded as suffering from Charcot-Marie-Tooth disease with diabetes mellitus as an

associated defect: (*a*) The reported association of the two maladies in the literature (*see* Table II). (*b*) A 14 to 19-year history of thin legs and foot deformity in VI (1) prior to the appearance of clinical diabetes mellitus. In the 120 cases of diabetic neuropathy cited by Goodman *et al.* (1953) the onset of neuropathy averaged 5·9 years after the onset of the diabetes; in only 4 did neuritic symptoms precede the diabetes. (*c*) The same authors state that the deformed foot in diabetic neuropathy typically tends to eversion, external rotation and flattening of the longitudinal arch. Our patient showed bilateral pes cavus and claw toes, typical of Charcot-Marie-Tooth disease.

In our series significant muscle wasting occurred in 4 cases of Friedreich's ataxia (*see* Table I) and (by definition) in all cases of peroneal muscular atrophy (Charcot-Marie-Tooth disease). In Case VII (1), suffering from Charcot-Marie-Tooth disease, muscle biopsy furnished features typical of muscle dystrophy and not neurogenic muscle atrophy. Greenfield *et al.* (1957) and Stephens, Hoover and Denst (1958) have reported similar occurrences. Spiller (1910) referred to autopsy findings of neurogenic and myopathic atrophy in the same patient suffering from Friedreich's ataxia. Biemond (1951) also noted progressive muscle dystrophy associated with Friedreich's ataxia. Van Bogaert (1948) emphasized the profound biological relations between neural hereditary degenerative tendencies and the progressive muscular dystrophies. The pathogenesis of these conditions remains obscure. Norman and Urich (1958) suggest that congenital hypoplasia affecting cerebellum, brain-stem and spinal cord may be allied to the later atrophy of vulnerable neuronal systems; both may be expressions of the same abiotrophic process.

Summary

From 21 pedigrees, a series of 40 patients are described to illustrate that members of the primary spinocerebellar atrophy group form, as it were, an unbroken chain linked by borderline and transitional cases.

Associated cardiac defect was present in 11 of 13 cases of Friedreich's ataxia, but was not confined to this disease. Of 4 cases of spastic paraplegia electrocardiographic abnormalities were present in 3 patients in 2 separate pedigrees, as well as in some of the relatives of these patients.

A number of other associated defects occurred in this series of patients: pes cavus, kyphoscoliosis, optic atrophy, colour blindness, external ocular palsies, epilepsy (*grand mal, petit mal*), myoclonic epilepsy, mental deficiency, paranoid trends, muscle dystrophy, diabetes mellitus, ichthyosis, hare-lip and cleft palate. The probable significance of these defects is discussed.

An analysis was made of some of the mechanisms possibly responsible for the mobile pes cavus encountered without spasticity in 3 patients with Friedreich's ataxia. It was concluded that muscle imbalance with pre-

ponderance of the tibialis posterior muscle seemed most likely to be the principal factor concerned.

ACKNOWLEDGMENTS

The authors would like to express indebtedness to their colleagues for freely referring patients: to Drs. K. Aaron, K. J. Murphy, O. W. Powell, A. Robertson, G. S. Stable, A. W. Steinbeck, D. J. Tuffley and L. D. Walters. Thanks are due also to Dr. M. J. Mead for pathological reports on Cases III (1), IV (2) and VII (1), to Dr. J. O'Reilly for performing an autopsy on Case IV (2), to Miss E. I. Flower for the co-operation of the Physiotherapy Department of the Brisbane Hospital and to Mr. E. Hollywood of Queensland University for the Photography. The authors would also like to thank the Editor of the *Lancet* for permission to refer to Pedigree XVII.

REFERENCES

ANDRÉ-VAN LEEUWEN, M. (1948) *Rev. Oto-Neuro-Ophtal.*, **20,** 43.
ASHBY, D. W., and TWEEDY, P. S. (1953) *Brit. med. J.*, **1,** 1418.
ASHENHURST, E. M., MILLAR, J. H. D., and MILLIKEN, T. G. (1958) *Brit. med. J.*, **2,** 415.
BELL, J. M., and CARMICHAEL, E. A. (1939) "Treasury of Human Inheritance." Vol. IV, Part 3. Cambridge Univ. Press.
BIEMOND, A. (1951) *Folia psychiat. neerl.*, **54,** 216.
VAN BOGAERT, L. (1948) *Encéphale*, **37,** 1.
—— (1951) *Rev. neurol.*, **84,** 121.
——, and MOREAU, M. (1939) *Encéphale*, **34,** 312.
BRAIN, W. R. (1947) "Diseases of the Nervous System." 3rd Edition, London.
BROWN, J. R. (1955) *In* "Clinical Neurology." Edited by Baker, A. B. Volume 2.
BRUCE, A. N. (editor) (1954) "Neurology." By S. A. Kinnier Wilson. 2nd Edition. London, Vol. II, p. 1078.
CARTER, H. R., and SUKAVAJANA, C. (1956) *Neurology*, **6,** 876.
CHANDLER, J. H., and BEBIN, J. (1956) *Neurology*, **6,** 187.
COLLIER, J. (1899) *Brain*, **22,** 71. Cited by Garland and Astley.
DEGENKOLB (1906) *Neurol. Zbl.*, **25,** 963. Cited by Bruce.
EVANS, W., and WRIGHT, G. (1942) *Brit. Heart J.*, **4,** 91.
FITZGERALD, G. W., and HYLAND, H. H. (1958) *Canad. med. Ass. J.*, **78,** 171.
FLEMING, R. (1957) *Neurology*, **7,** 476.
GAREISO, A., and PEDACE, E. A. (1948) *Arch. argent. Pediat.*, **30,** 73.
GARLAND, H. G., and ASTLEY, C. E. (1950) *J. Neurol. Neurosurg. Psychiat.*, **13,** 130.
GOODMAN, J. I., BAUMOEL, S., FRANKEL, L., MARCUS, L. J., and WASSERMANN, S. (1953) "The Diabetic Neuropathies." Springfield, Ill.
GREENFIELD, J. G. (1954) "The Spino-cerebellar Degenerations." Oxford.
——, BLACKWOOD, W., MCMENEMEY, W. H., MEYER, A., and NORMAN, R. M. (1958) "Neuropathology." London.
——, SHY, G. M., ALVORD, E. C., and BERG, L. (1957) "An Atlas of Muscle Pathology in Neuromuscular Diseases." Edinburgh.
HARRIMAN, D. G. F., and MILLAR, J. H. D. (1955) *Brain*, **78,** 325.
HOLMES, G. M. (1910) "Familial and Hereditary Ataxia." *In* Allbutt and Rolleston's System of Medicine. London. **7,** 770. Cited by Greenfield.
HUNT, J. R. (1921) *Brain*, **44,** 490.

XUM

JENDRASSIK, E. (1902) *Dtsch. Z. Nervenheilk.*, **22,** 444. Cited by Poser, Dewulf and van Bogaert.
JÉQUIER, M. (1948) *Rev. Oto-Neuro-Ophtal.*, **20,** 431.
KENDALL, H. O., and KENDALL, F. P. (1949) "Muscles, Testing and Function." Baltimore.
KNIGHT, R. A. (1949) *In* "Campbell's Operative Orthopædics." Edited by Speed, J. S., and Smith, H. 2nd Edition. St. Louis. Volume II, pp. 1287, 1296.
LAKE, N. C. (1935) "The Foot." London.
MAKIN, M. (1958) *Ann. R. Coll. Surg. Engl.*, **22,** 1.
MALAMUD, N., and COHEN, P. (1958) *Neurology*, **8,** 261.
MATTHEWS, W. B. (1950) *J. Neurol. Neurosurg. Psychiat.*, **13,** 307.
NORMAN, R. M., and URICH, H. (1958) *J. Neurol. Neurosurg. Psychiat.*, **21,** 159.
POSER, C. M., DEWULF, A., and VAN BOGAERT, L. (1957) *J. Neuropath.*, **16,** 209.
RAYMOND, F. (1905) *Nouv. Iconogr. Salpêt.*, **18,** 121. Cited by Greenfield.
ROTH, M. (1948) *Brain*, **71,** 416.
ROUSSY, G., and LÉVY, G. (1926) *Rev. neurol.*, **1,** 427.
——, —— (1932) *Pr. méd.*, **40,** 1733.
RUSSELL, D. S. (1946) *J. Path. Bact.*, **58,** 739.
SCHLEZINGER, N. S., and GOLDSTEIN, K. (1940) *N.Y. St. J. Med.*, **40,** 415. Cited by Ashby, D. W., and Tweedy, P. S. (1953) loc. cit.
SJÖGREN, T., and LARSSON, T. (1957) *Acta psychiat., Kbh.*, **32,** suppl. 113. Cited in *Lancet*, 1957, **2,** 377.
SPILLANE, J. D. (1940)*Brain*, **63,** 275.
SPILLER, W. G. (1910) *J. nerv. ment. Dis.*, **37,** 411. Cited by Matthews.
STEPHENS, J., HOOVER, M. L., and DENST, J. (1958) *Brain*, **81,** 556.
STEWART, R. M. (1959) *Scot. med. J.*, **4,** 84.
SUTHERLAND, J. M. (1957) *Lancet*, **2,** 169.
SYMONDS, C. P., and SHAW, M. E. (1926) *Brain*, **49,** 387.
WILES, P. (1955) "Essentials of Orthopædics." 2nd Edition.

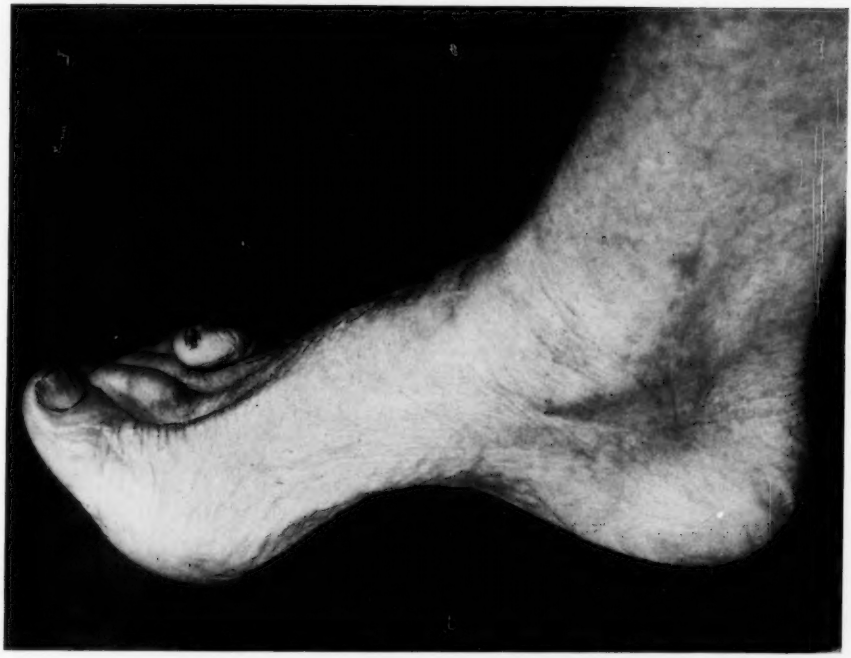


FIG. 1 (*Case I* (1)).—Familial pes cavus, showing the typical foot deformity.

FIG. 2 (*Case IV* (2)).—Charcot-Marie-Tooth disease. Overlying the lower half of the spinal cord, the pia and arachnoid matter showed adhesions and densely calcified plaques. (Scale reading in centimetres.)

To illustrate article by J. H. Tyrer and J. M. Sutherland.

XUM

FIG. 3A (*Case VII* (1)).—Showing ichthyosis (volar aspect of left forearm).

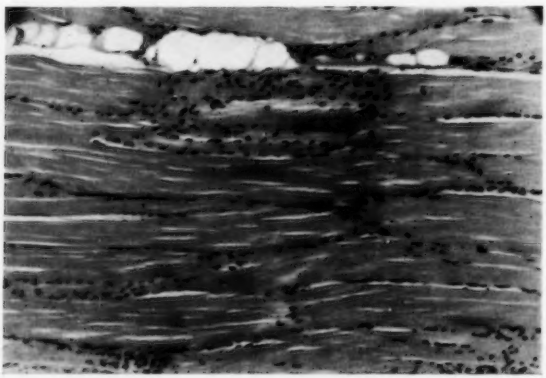


FIG. 3B (*Case VII* (1)).—Section from left peroneal muscle group (× 110), showing proliferation of sarcolemmal nuclei and infiltration of fat cells between muscle fibres, changes typical of muscle dystrophy.

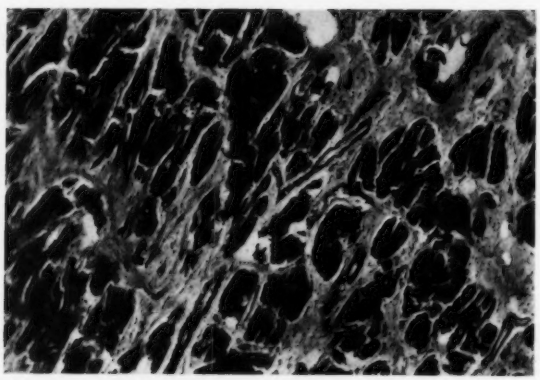


FIG. 4 (*Case XIII* (1)).—Friedreich's ataxia. Section of myocardium of left ventricle showing interstitial fibrosis. (× 75.)

To illustrate article by J. H. Tyrer and J. M. Sutherland.

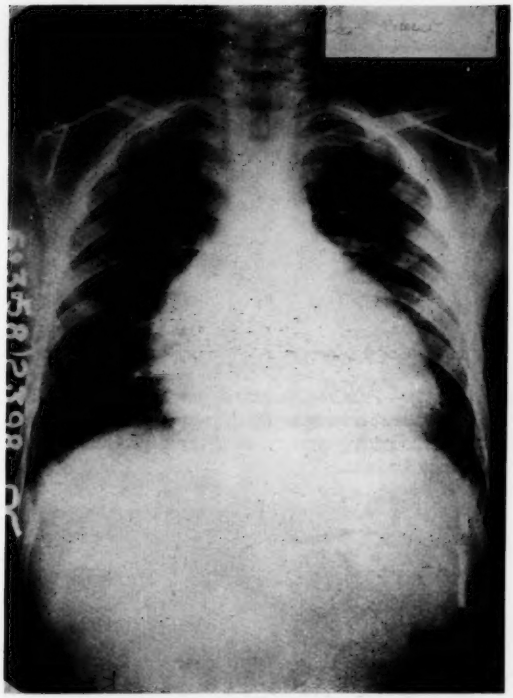


FIG. 6 (*Case XVI* (1)).—Spastic paraplegia. Skiagram of the chest showing cardiomegaly.

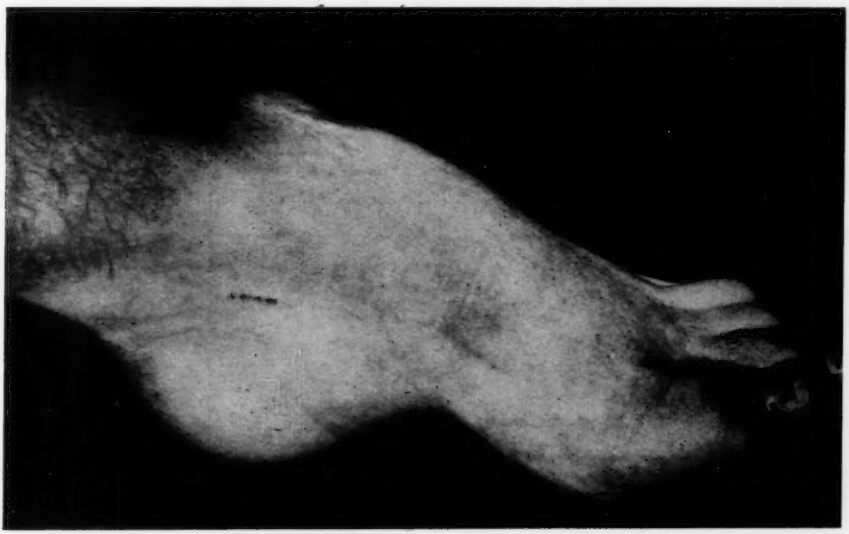


FIG. 7 (*Case XII* (3)).—Friedreich's ataxia, showing the characteristic foot deformity. This patient was a cousin of Case XII (1) whose foot is shown in fig. 8A.

To illustrate article by J. H. Tyrer and J. M. Sutherland.

XUM

FIG. 8A (*Case XII* (1)).—Friedreich's ataxia (cousin of Case XII (3), whose foot is shown in fig. 7). The patient is lying so that the lateral aspect of the left foot rests on a horizontal surface, eliminating gravity as a force producing foot deformity; the "dropped" forefoot may be seen.

FIG. 8B (*Case XII* (1)).—The foot deformity is held corrected by a block of wood and a weight of 10 kg.

FIG. 8C (*Case XII* (1)).—Weak faradic stimulation of the tibialis posterior muscle caused drawing down of the forefoot and displacement of the block of wood.

To illustrate article by J. H. Tyrer and J. M. Sutherland.

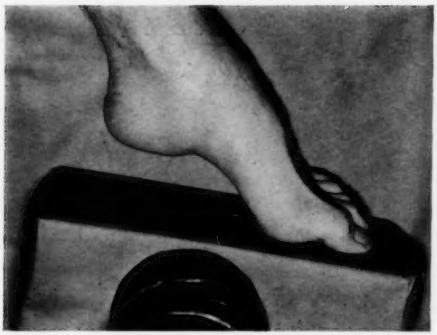


FIG. 8D (*Case XII* (1)).—As fig. 8C, but a little later.

FIG. 8E (*Case XII* (2)).—Weak faradic stimulation of the peroneus longus muscle also caused drawing down of the forefoot and displacement of the block of wood.

FIG. 8F (*Case XII* (1).—As fig 8E, but a little later.

To illustrate article by J. H. Tyrer and J. M. Sutherland.

DISTANT METASTASES FROM MEDULLOBLASTOMA OF THE CEREBELLUM

BY

EDITH PATERSON

Christie Hospital, Manchester, 20

THE possibility of distant metastases from cerebellar medulloblastoma occurring outside the central nervous system has been reported in a very few cases. There has been a reluctance to accept that the primary tumour in these cases was in fact a medulloblastoma. The following 7 cases are, therefore, reported. They have occurred among the patients referred by neurosurgeons for radiotherapy at the Christie Hospital, Manchester, over the last eleven years. Since, in these cases the occurrence of distant metastases is not in question, the pathological diagnosis of the primary tumour is of the first importance. Because the histogenesis of this tumour is controversial it is felt that dogmatism about the diagnosis is out of place. Considerable care has, therefore, been taken to quote the opinions of the various pathologists whose help has been sought. The cases are presented in the belief that they will add to the occasional reports of similar cases in the literature.

In the earlier cases quoted here the pathological diagnosis was made by the late Dr. Eugen Pollak, Neuropathologist to the University Neurosurgical Unit, Manchester. Since his death the material from more recent cases has been submitted to a panel of pathologists, in addition to the pathologists at the hospital concerned with the individual case.

In the histories which follow the radiotherapy has not been specified in detail. All cases were treated similarly. The whole central nervous system was irradiated as a single volume, to a dose of 3000 r (2700 rads) given over three weeks. When this method of treatment was published (Paterson and Farr, 1953), 3 cases were described as having died with distant metastases. These cases are included here.

Case 1.—J. O'B. 47/5348.

This 8-year-old boy had a history of vomiting and listlessness, followed by headaches, squint, and ataxia. One month after the symptoms first developed, an operation by Mr. R. A. Bailey at Crumpsall Hospital revealed a large tumour of the vermis, extending into the fourth ventricle. The tumour was macroscopically removed, and reported by Dr. Pollak as medulloblastoma. The child was well for several months, then symptoms recurred, and he was referred for radiotherapy. Great improvement followed this, and he seemed to be well. However, seven months after therapy he complained of pain

in the thigh and was feverish. The upper end of the thigh was swollen and hot, and an X-ray showed periostitis and cortex changes in the upper end of left femur. A biopsy of the femur showed "an undifferentiated tumour, could be neuroblastoma" (Dr. Helen Russell, pathologist to the Christie Hospital). This lesion extended rapidly, and others appeared in left petrous temporal, right femur and tibia, right and left humerus, mandible, pelvis, ribs and scapulæ.

Most of the lesions were treated palliatively by irradiation to relieve pain; the lesions were radiosensitive.

The child died of a pulmonary infection seven months after the first appearance of metastases. Autopsy findings (Dr. H. Russell)—

The Central Nervous System showed residual tumour in a scarred lesion of the vermis. Extradural deposits of tumour were present in the cervical, lower lumbar and sacral region, and leptomeningeal deposits at the level of first, second and third thoracic segments. These lesions were reported to be medulloblastoma.

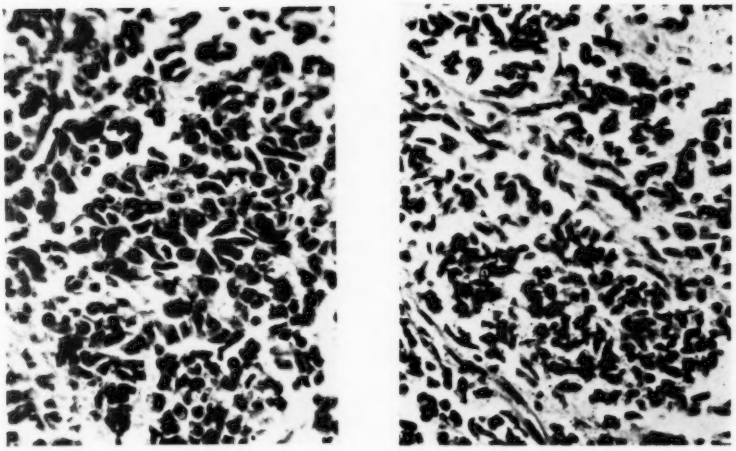
Deposits outside the Central Nervous System. These were present in the *skull bones*, and in the laminæ and spinous processes of the lower thoracic and upper lumbar *vertebræ*. Almost every *rib* was encased in tumour. *Lymph nodes* were invaded. These included the jugular group on both sides, and the supraclavicular nodes on the left side. In the abdomen the para-aortic and right external iliac group were invaded. No tumour was present in the lungs, liver, pancreas, spleen, suprarenal glands, kidneys, bladder or testes. The pathologist considered that the tumour in all the metastases appeared much the same, and that dissemination via the paravertebral venous network was likely. That final histological diagnosis was medulloblastoma (figs. 1A, 1B, 8, Plate XXXVII).

Case 2.—J. H. 49/1301.

At the age of 19 years this patient developed headaches, vomiting, and difficulty in walking. A diagnosis of cerebellar tumour was followed by partial operative removal by Professor Geoffrey Jefferson, at Manchester Royal Infirmary. The tumour was solid and was seen to be enlarging the left cerebellar tonsil, and extended to the superior cerebellar surface. It was considered clinically to be a medulloblastoma. This tumour was first considered by Dr. Pollak to be a medulloblastoma, but some years later he decided it as a hæmangioblastoma. A course of localized irradiation followed the operation. He remained well for nine years when his symptoms recurred. The tumour removed at this second operation was diagnosed by Dr. Pollak as a medulloblastoma, and to be similar to the first tumour which he evidently now thought to be of that nature. The patient was given a course of radiotherapy and improved very much, so that the only residual symptom was left-sided nystagmus. Twenty-two months after irradiation the patient was admitted to hospital with pain in the lumbosacral area and severe anæmia. The hæmoglobin was 36 per cent, the red cell count was 2,000,000 per c.mm., and the white count normal. The serum alkaline phosphatase was 18·0 units/100 ml. Radiography of the bones revealed widespread lesions in ribs, vertebræ and pelvis. These were regarded by the radiologist as typical of metastases spread by the blood stream, and it was considered that the bone involvement was sufficiently widespread to account for his anæmia. There were no metastases present in the lungs. The patient died eight months after the appearance of metastases. No autopsy was carried out. The final diagnosis was considered to be medulloblastoma (figs. 2 and 9).

Case 3.—J. K. 50/2277.

This boy of three-and-a-half years had listlessness and vomiting for two months, followed by papillœdema and sixth nerve weakness. After admission to hospital the child deteriorated rapidly, became drowsy, and had a highly abnormal electroencephalo-



A B

FIG. 1 (*Case* 1).—J. O'B. A, Cerebellar tumour (biopsy). × 500 H. and E. B. Secondary tumour in femur (biopsy) × 500 H. and E.

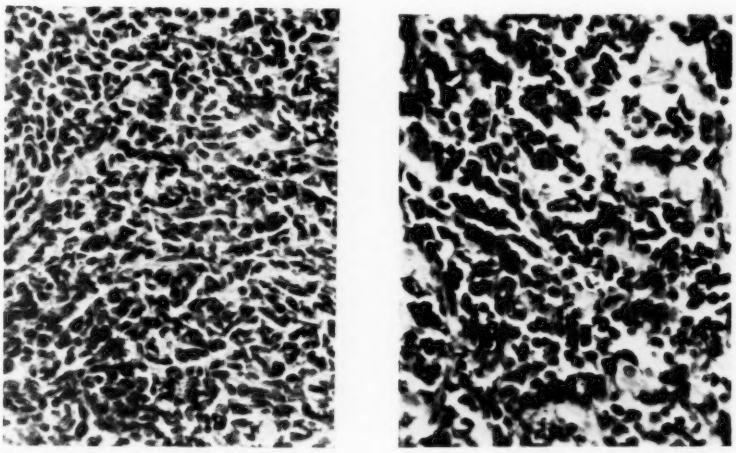


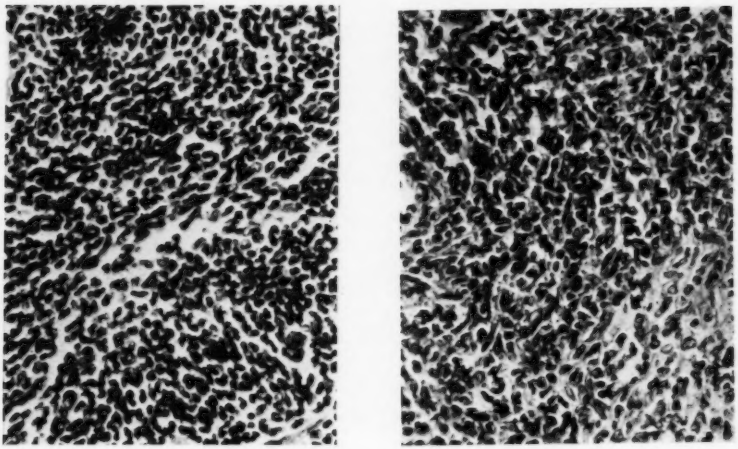
FIG. 2 FIG. 3

FIG. 2 (*Case* 2).—J. H. Cerebellar tumour (biopsy). × 500 H. and E.

FIG. 3 (*Case* 3).—J. K. Secondary tumour from biopsy of supraclavicular lymph node. × 500 H. and E.

To illustrate article by Edith Paterson.

XUM



A B

FIG. 4 (*Case* 4).—A. S. A, Cerebellar tumour (autopsy). × 500 H. and E. B, Secondary tumour in lymph node (autopsy). × 500 H. and E.

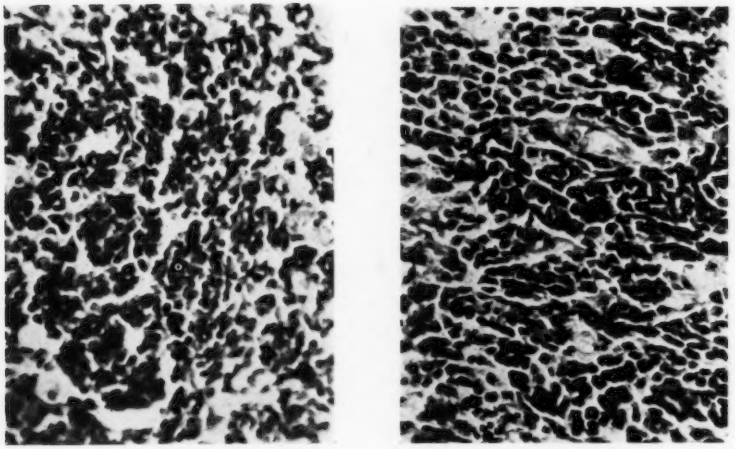
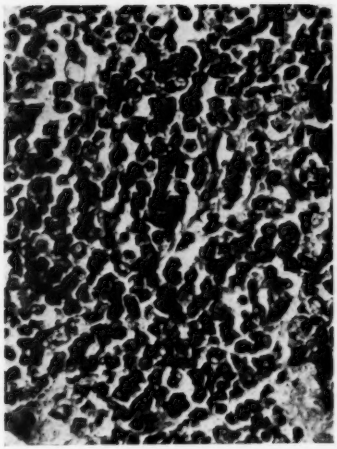


FIG. 5 FIG. 6

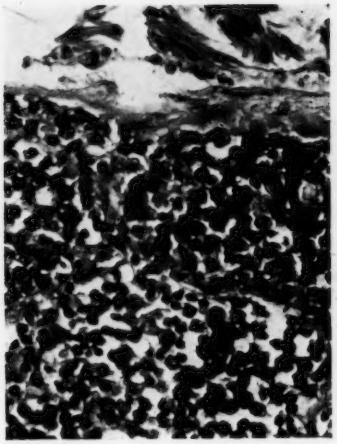
FIG. 5 (*Case* 5).—N. N. Cerebellar tumour (biopsy). × 500 H. and E.

FIG. 6 (*Case* 6).—M. H. Cerebellar tumour (biopsy). × 500 H. and E.

To illustrate article by Edith Paterson.



A



B

FIG. 7 (*Case* 7).—P. D. A, Secondary tumour in liver (autopsy). × 500 H. and E. B. Secondary tumour in lymph node (autopsy). × 500 H. and E.

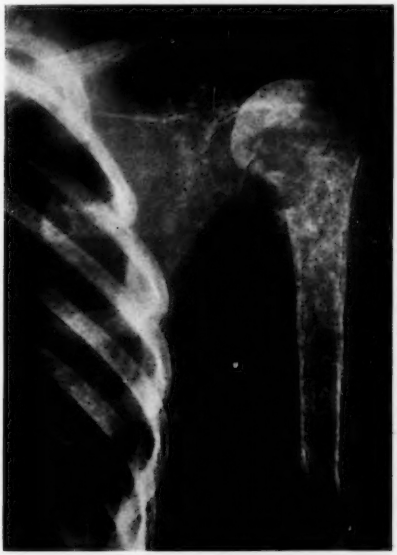


FIG. 8 (*Case* 1).—J. O'B. Widespread secondary tumour in humerus, shoulder girdle and ribs. Shows sun-ray spicules.

To illustrate article by Edith Paterson.

XUM

FIG. 9

FIG. 10

FIG. 9 (*Case* 2).—J. H. Widespread secondary tumour. Osteolytic and osteosclerotic changes.

FIG. 10 (*Case* 3).—J. K. Pathological fracture right femur. Tumour has destroyed left wing of sacrum.

FIG. 11 (*Case* 5).—N. N. Extensive secondary tumour right femur. Shows elevation of periosteum.

To illustrate article by Edith Paterson.

gram. An emergency decompression done by Professor Geoffrey Jefferson at Manchester Royal Infirmary showed the cerebellar tonsils to be pushed down through the foramen magnum and two small nodules were seen on the surface of the cerebellar hemisphere. These were regarded as arising from a deeper tumour. No attempt at removal was made. A biopsy specimen obtained from one of the nodules was unfortunately lost. Radiotherapy was given on the basis of Professor Jefferson's diagnosis of medulloblastoma. The child, at this time, was semi-stuporous and convulsions were frequent; the decompression was bulging, and papillœdema was present. He improved greatly after radiotherapy, and was able to ride his tricycle. However, six months after treatment he became irritable and developed a swelling 3 cm. in diameter in the left side of neck, another 5 cm. long over the left nipple, and complained of pain in both legs.

A biopsy of the supraclavicular mass was carried out. The tumour was reported by Dr. H. Russell as being undifferentiated, and could be of the neuroblastic cell type. Dr. Pollak reported that "gland section contains tumour; think it is medulloblastoma."

Radiography of bones showed metastases in a rib, in the neck of right femur which was fractured, the left ilium, and probably the sacrum. The lungs were not involved.

The child died a month after the appearance of metastases. There was no autopsy. The final diagnosis was medulloblastoma (figs. 3 and 10).

Case 4.—A. S. 51/0304.

This girl aged 4 years came with a history of vomiting and loss of weight for four months, followed by failing eyesight and squint, nystagmus, and ataxia. An exploration by Mr. Connolly at the Royal Victoria Hospital, Belfast, revealed a greyish friable tumour in the left cerebellar hemisphere; it also involved the dura. The histology was reported by Professor J. Henry Biggart of Belfast as typical medulloblastoma. Deep X-ray therapy followed and the child thereafter was improved but was unable to walk and appeared blind.

Twelve months thereafter the child's general condition deteriorated; she complained of pain in the back and limbs. There was generalized lymphadenopathy, and obstruction of the portal and inferior vena caval circulation. Radiographs showed areas of destruction in the shoulder girdle, vertebræ, ribs and pelvis, suggestive of secondary deposits. A further biopsy was done.

Two weeks after readmission to hospital the patient died of a terminal aspiration pneumonia. An autopsy was performed by Dr. A. Crawford of the Northern Ireland Fever Hospital, Belfast, with the following findings:

Cranial cavity.—Widespread tumour invasion of base of brain with dural adhesion. Following fixation, coronal sections of the brain showed invasion by soft tumour tissue of the undersurface of cerebellum and cerebral hemispheres. Moderate hydrocephalus was present. Histologically tumour infiltration extended into brain tissue. A section through the aqueduct of Sylvius showed a mass of tumour which had ruptured through ependyma.

Some areas of degeneration and necrosis were present in tumour tissue. Sections from various areas stained by Ranson's method did not show nerve fibrils. The medulla was relatively unaffected but gelatinous exudate was present on the pial surface of the cervical cord, and in the cauda equina a few dark cells were present resembling those of the tumour.

Distant metastases.—Extensive tumour deposits were found in the *abdominal parietes* and *retroperitoneal tissues*. The tumour occluded the left ureter and constricted the inferior vena cava. The deposits extended down to the pelvis, whilst posteriorly they invaded the vertebral bodies which were honeycombed with tumour. *Lymph nodes* at the pelvic brim were replaced with tumour.

XUM

In the *ovary*, a cleft near the hilum was full of tumour cells. Tumour nodules were present in the *right kidney*; the tumour cell was small with an oval rather dark nucleus and scanty indistinct cytoplasm. Some lymphatics around branches of the renal artery were full of tumour cells. The *left kidney* was hydronephrotic and the *left ureter* showed invasion of the wall. Some lymphatics near the pelvis and around blood vessels were full of tumour cells, and there was patchy infiltration of the parenchyma by tumour.

Sections of *vertebral bodies* showed practically no normal bone-marrow cells but replacement with tumour cells. Multiple secondaries were present in the *ribs*.

The lungs, thyroid gland, liver, spleen, pancreas, and adrenals were free of tumour.

The final diagnosis here was medulloblastoma (fig. 4A and B).

Case 5.—N. N. 55/4436.

This 3-year-old boy had a history of vomiting and unsteady gait for six weeks. An exploration was carried out by Mr. R. T. Johnson at the Manchester Royal Infirmary, and a reddish-grey tumour displacing the cerebellar tonsils was found. The vermis was split and a large quantity of soft vascular tumour was removed by suction. The diagnosis of medulloblastoma was made by Dr. P. O. Yates, the neuropathologist, and by all six members of the panel of pathologists to whom the sections were submitted.

Two weeks after the exploration the child had radiotherapy to the central nervous system. He improved greatly, but the occipital loculus remained prominent. Eight months later, he was readmitted to the neurosurgical unit with symptoms of multiple metastases. There was no evidence of a block of cerebrospinal circulation but the child was very ill, with pains in the legs. The lymph nodes in the neck and inguinal regions were enlarged, and there were masses on the scalp. X-rays showed widespread bone metastases in the pelvis, both femora, humeri and forearm bones. The skull was involved from the outside. No metastases were visible in the X-rays or lungs or vertebræ. The child died at home six weeks later, and there was no post-mortem. The final diagnosis in this case was medulloblastoma (figs. 5 and 11).

Case 6.—M. H. 58/4026.

This boy, aged 2 years, had a one-month history of lack of appetite, shakiness and holding his head in his hands. An exploration by Mr. A. N. Guthkelch at the Royal Manchester Children's Hospital, revealed a bulging cerebellum with a broad vermis. A tumour was just visible between the cerebellar tonsils. The vermis was split and the tumour was removed by suction and diathermy. A diagnosis of medulloblastoma was made by the four pathologists consulted.

The child was given deep X-ray treatment. His general condition and his ataxia improved with treatment, but he remained irritable and disturbed. Three months later he was brought back to hospital very ill, listless, and not eating. Masses were present in the anterior part of the scalp, and over the right sacroiliac joint; these were seen in the X-ray to be unrelated to bone destruction. The child died suddenly a few days later, and death was believed to be due to an intracranial hæmorrhage. There was no autopsy. The final diagnosis was medulloblastoma (fig. 6).

Case 7.—P. D. 58/4475.

This 2-year-old boy had a history of ataxia for four months; for three months he had been subject to vomiting and lost the ability to walk or stand. On admission in the care of Mr. R. T. Johnson at the Manchester Royal Infirmary, a ventriculogram showed a space-occupying lesion of the posterior fossa with dilated ventricles. Craniotomy and decompression were done. Some resistance was felt when the cerebellum was

needled. As the vermis was brought into view a large tortuous blood vessel was seen. This was thought to be either a vascular malformation or associated with a highly vascular tumour beneath. Owing to the child's condition, no further exploration was possible.

He was given radiotherapy on a clinical diagnosis of medulloblastoma. When this started the child was unable to stand without assistance, he had slight facial weakness, and the occipital region was bulging. Daily aspiration of cerebrospinal fluid was necessary for a time. There was an immediate improvement with treatment, the decompression bulge became smaller, vomiting ceased and the child started walking again. However, he was brought back three months later, irritable, with enlarged nodes and signs of general metastases in bone. The hæmoglobin was 58 per cent, the white cell count being within normal limits, and of normal appearance. The child died in hospital five weeks after the appearance of metastases. During this time the hæmoglobin level fell, the white cell count remained normal but the platelet count was low. Terminally he developed tumour masses round the mouth.

An autopsy was done by Dr. M. Levene at the Christie Hospital. He found a tumour in the cerebellum which he considered to be primary, and a terminal dissemination to bone-marrow, lymph nodes and elsewhere. The details are as follows:

Central nervous system.—A necrotic cerebellar tumour composed of small round cells was found in the midline. Deposits in the *dura* and *subdural* surface were present only at the site of operation. The rest of the central nervous system was not involved.

Metastases elsewhere.—Tumour similar to the above was found replacing the bone marrow of *vertebræ*, *ribs* and *sternum*. Tumour masses were present in the *pelvis*. The *lymph nodes* of axillae, groins and the common iliac group, were invaded. Tumour was present in the *parotids*, the *pancreas*, and the *liver*. No tumour was found in the lungs, testicles, thyroid, suprarenals, kidney, spleen, tonsil, submandibular lymph nodes or the gut.

The pathologist considered the tumour to be a medulloblastoma of the cerebellum. Slides of the autopsy material from brain, bones and lymph nodes were submitted to a panel of pathologists. All six pathologists considered the tumour to consist of undifferentiated round cells. This was interpreted variously as medulloblastoma, neuroblastoma, and in one instance as lymphosarcoma, and in another Ewing's tumour. The final diagnosis here was medulloblastoma (figs. 7A and 7B).

Discussion

These cases illustrate the occurrence of distant metastases in a group of cerebellar tumours which seem to fit in with the label of medulloblastoma. The clinical criteria of our cases are in accord with this diagnosis. Those include the incidence in young people, the site of the tumour, and its radiosensitivity. In the three cases in which autopsy was done the primary tumour in the cerebellum had recurred or was still present; metastases within the central nervous system in Cases 1 and 4 demonstrated also the classical meningeal spread of medulloblastoma.

Not only did the clinical picture correspond to that given by Bailey and Cushing, the reports on the histology also resembled closely the original descriptions (Bailey and Cushing 1925). These authors were impressed by "the structureless arrangement of the tumour cells," and illustrated ball-like arrangements of cells, similar to our cases. The elongated cell is also a familiar finding as is the occasional pseudorosette. Kernohan and Sayre

XUM

(1952) were also impressed by the inconstancy of medulloblastoma: "in some of these tumours the nuclei are larger and have blunter ends and the cytoplasm does not taper off at one end. In other variants the nuclei tend to become rounder and at times even quite round."

The diagnosis of medulloblastoma seems to rest on the clinical findings and the histological picture which is sometimes remarkably isomorphic but varies considerably from case to case, showing with suitable and fortunate staining the rare occurrence of spongioblastic or neuroblastic differentiation (Russell and Rubinstein, 1959).

The histological similarity between medulloblastoma and neuroblastoma of the sympathetic nervous system will be recalled. Indeed, before Cushing and Bailey named the medulloblastoma, the earlier cases occurring at the Peter Bent Brigham Hospital were classified as neuroblastoma of the cerebellum. It might be thought from this histological similarity that the cerebellar tumours could be secondary neuroblastoma from an unknown primary. There is no evidence for this in these 7 cases, or in those recorded in the literature; nor have I ever seen a secondary appearing in the cerebellum from a neuroblastoma occurring in the accepted sites. In none of these cases was calcification present in the soft-tissue masses. Bone metastases are a feature both in the disseminated neuroblastomas and in these medulloblastomas, although of course such spread is a sequel to blood-borne dissemination of many other tumours.

Histologically the 7 cases were diagnosed by the same methods (and largely by the same pathologists) as the remainder of the cases which have been treated over the last twenty-six years by radiotherapy which was limited to the central nervous system, and which has yielded a reasonably good five-year survival rate (Paterson, 1958). The 7 cases quoted here seem to be part of the larger group.

The possibility of distant metastases in medulloblastoma is not generally recognized although it has been reported on several occasions. It is of interest to compare the sites of distant spread shown in Table I with the findings of previous observers. The common sites, bones, lymph nodes, and connective tissue are echoed in other reports. In none of the reported cases have metastases been present in the lungs; this agrees with our failure to find any lung tumours either by radiological examination or at autopsy.

In the earliest report Wohlwill (1930) described an infant with medulloblastoma and a tumour in a supraclavicular node. The writer concluded with some hesitation that the tumour in the lymph node was metastatic. In Nelson's case (1936) the metastases were limited to vertebræ. Two cases have been reported by Zülch (1956). In both of these there were metastases to vertebræ; in one, additional deposits were present in skin, and in the other in pelvic tissues. In the case recently described by Rubinstein (1959) the bones, retro-orbital tissues, and lymph nodes were invaded.

TABLE I.—SITE OF METASTASES IN TISSUE AND ORGANS OUTSIDE CENTRAL NERVOUS SYSTEM

	Bones	*Connective tissue*	*Lymph nodes*	*Abdominal and pelvic organs*	*Lungs*
1 J. O'B.	Femora, tibiæ, humeri, jaw, skull (petrous temporal) ribs, scapulæ	Abdominal wall, parietal pleura	Lower jugular bilateral, left supraclavicular, right external iliac, para-aortic	Nil	Nil
2 J. H.	Ribs, vertebræ, pelvis				Nil
3 J. K.	Rib, right femur, left ilium and wing of sacrum	Chest wall	Left supraclavicular, left groin		Nil
4 A. S.	Ribs, scapulæ pelvis vertebræ	Retro-peritoneal	Generalized	Myometrium ovary, kidney	Nil
5 N. N.	Pelvis, femora, humeri, forearm bones, skull	Scalp	Cervical and inguinal		Nil
6 M. H.	Nil—examination limited	Scalp, tissue over sacro-iliac joint			Nil
7 P. D.	Vertebræ, iliac bones, sternum, ribs	Around mouth and parotid glands	Neck, axillæ, groins, and common iliac	Liver, pancreas	Nil

This case resembles our Case 4 in that the tumour was growing back into the irradiated brain and cerebellum from the meninges.

The 7 cases reported here have occurred over eleven years of observation; during the same period a total of 35 microscopically confirmed medulloblastomas have been seen at the Christie Hospital. During the past twenty-six years the author has seen a total of 50 such cases and whilst none with distant metastases was found in the earlier examples, it has not been possible to ascertain the exact cause of death in a few of these who died elsewhere. It is not therefore possible to arrive at an accurate figure for the incidence of distant metastases from medulloblastoma. In the 13 cases described by Bailey, Buchanan and Bucy in 1939, no instance of distant metastases was found in the 7 cases on which an autopsy was performed. However, in 3 of these the examination was limited to the central nervous system.

How distant metastases may arise is illustrated in our 3 cases in which autopsy was done. All 3 showed penetration of the dura. A similar spread may have been present in the remainder, either at the time of treatment, or before, or as part of the recurrence of the tumour. Tumour cells penetrating the dura would then spread by invasion of blood vessels. Local lymphatic extension to the extracranial tissues of head and neck is suggested by those cases which demonstrated either scalp masses or cervical

XUM

lymph node involvement (Table I). The association of a dural infiltration and distant metastases was also shown in the case reported by Rubinstein.

Considering the spreading nature within the central nervous system of the tumour we know as medulloblastoma, it is remarkable that remote metastases are seen so seldom. It may thus be deduced that either operative interference or radiotherapy of the tumour has determined the spread, but as most cases of cerebellar tumours are treated by surgery, or radiotherapy, or both, it is impossible to find cases for comparison. However, to assist speculation along these lines Table II gives the time-interval

TABLE II.—INTERVAL BEFORE APPEARANCE OF DISTANT METASTASES

Cases	*From start of symptoms (months)*	*From time of operation (months)*	*From time of commencement of x-ray therapy (months)*
1 J. O'B.	13	12	7
2 J. H.	26	25	22
3 J. K.	9	7	6
4 A. S.	17	13	12
5 N. N.	10	9	8
6 M. H.	5	4	3
7 P. D.	8	4	3

preceding the first symptom of metastasis, calculated from the date of surgery and from the commencement of radiotherapy. In two cases evidence of metastasis occurred particularly quickly (Cases 6 and 7). In Case 6 distant metastases were undoubtedly present three and a half months after surgery, and only two months after the termination of the radiotherapy course. In Case 7, another young child, the history was also very brief. It is possible in both these cases that the seeding had occurred before treatment.

It is hoped that this account of these unusual cases will focus interest on the possibility of distant metastases from this cerebellar tumour of young people. Reports of future cases may then help to demonstrate the factors which determine systemic spread and the mode of dissemination.

SUMMARY

A description is given of seven cases of cerebellar tumours regarded as medulloblastoma. These cases developed distant metastases. The common sites were bone, soft connective tissue, and lymph nodes. The possible mode of spread is discussed.

ACKNOWLEDGMENTS

I wish to acknowledge the great help given by the many pathologists whose advice has been sought. In addition to those mentioned in the text I wish to thank those pathologists who constitute a panel for the Manchester

Children's Tumour Registry. These include Professor A. C. P. Campbell of Manchester, Professor Rupert Willis, Dr. Sydney Farber of Boston, Mass., Dr. Agnes Macgregor of the Sick Children's Hospital, Edinburgh, Dr. H. B. Marsden of the Royal Manchester Children's Hospital, and Dr. P. O. Yates, Senior Lecturer in Neuropathology, University of Manchester. I thank also Dr. J. K. Steward, the Registrar to the Children's Tumour Registry, for his help, especially in obtaining the pathological material. My warm thanks are due to Sir Geoffrey Jefferson, not only for the critical reading of the manuscript but for much help over many years in the interesting problems associated with the treatment of medulloblastoma cases. I am indebted to Mr. Mowat for the photomicrographs.

REFERENCES

BAILEY, P., BUCHANAN, D. N., and BUCY, P. C. (1939) "Intracranial Tumors of Infancy and Childhood." Chicago.

——, and CUSHING, H. (1925) *Arch. Neurol. Psychiat., Chicago*, **14,** 192.

KERNOHAN, J. W., and SAYRE, G. P. (1952) "Tumors of the Central Nervous System." *In* Armed Forces Institute of Pathology. Atlas of Tumor Pathology, Sect. X, Fasc. 35 and Fasc. 37. Washington, D. C.

NELSON, A. A. (1936) *Amer. J. Cancer*, **28,** 1.

PATERSON, E. (1958) *J. Fac. Radiol.*, **9,** 170.

——, and FARR, R. F. (1953) *Acta radiol., Stockh.*, **39,** 323.

RUBINSTEIN, L. J. (1959) *J. Path. Bact.*, **78,** 187.

RUSSELL, D. S., and RUBINSTEIN, L. J. (1959) "Pathology of Tumours of the Nervous System." London.

WOHLWILL, F. (1930) *Z. ges. Neurol. Psychiat.*, **128,** 587.

ZÜLCH, K. J. (1956) "Biologie und Pathologie der Hirngeschwülste." *In* Handbuch der Neurochirurgie. edited by H. Olivecrona and W. Tönnis. Berlin. Vol. 3, p.1.

XUM

BRAIN LIPIDS IN MULTIPLE SCLEROSIS AND OTHER DISEASES[1]

BY

B. GERSTL,[2,3] M. J. KAHNKE,[2] J. K. SMITH[2], M. G. TAVASTSTJERNA,[2] AND R. B. HAYMAN[2]

SEVERAL hypotheses on the ætiology of multiple sclerosis (MS) and their merits have been reviewed recently by Kurland *et al.* (1955), Thompson (1959), and Miller and Schapira (1959), with each of these reviews arriving at a different conclusion. The observations favouring a metabolic disorder (Thompson, 1959) as the underlying cause have been supported by the reports on increase of neuraminic acid (Cumings, 1955; Plum and Hansen, 1960) in the brain, increased vitamin levels in the cerebral spinal fluid (Sobotka *et al.*, 1958) and reduced ability by the MS patient to retain vitamin B_{12} (O'Connor *et al.*, 1960).

Alterations of the lipids in the central nervous system (CNS) in MS have been reported by Brante (1949), Cumings (1953, 1955) and Plum and Hansen (1960). The appearance of a lipoprotein with abnormal mobility in the cerebral spinal fluid (Smith *et al.*, 1956) and the different poly-unsaturated fatty acid (PUFA) ratios in the plasma of MS patients when compared with controls (Gerstl *et al.*, 1959) seemed to point to the fatty acids, particularly the PUFA, which are unique components of the cerebral phosphatides (Klenk and Debuch, 1959), as a fruitful area for investigation.

It was fortuitous that a case where the MS lesions were largely limited to the spinal cord could be included in this study, thereby providing an unusual opportunity to search for chemical alterations in areas relatively remote from histologically identifiable lesions. The lipid chemistry of the brain in other than CNS diseases has not been subject to study as far as could be ascertained. On the assumption that neurologic disorders and demyelination in tumour patients without demonstrable metastases to the CNS (Brain *et al.*, 1951; Åström *et al.*, 1958) might also

[1]Supported by the U.S. Veterans Administration, and by U.S. Public Health Service Grant No. B–1667.

[2]From the Veterans Administration Hospital, Oakland, Calif., and

[3]Department of Pathology, School of Medicine, University of California, San Francisco, Calif.

involve metabolic factors, examples of such brains were included in this study. The brain of a case of long-standing malnutrition was also subjected to analysis.

Quantitative data on PUFA have been given only for total brain (Klenk and Montag, 1958). Consequently, values were established separately for the lipids of cortex and white matter of human brain. The rather large quantities of material needed for the analytic procedures required that tissues from various areas (frontal, parietal and occipital lobes) be pooled, though they may vary as to content of different lipids. On four brains, plasmalogens were also determined.

Materials and Methods

Brain tissue was obtained at autopsies. Diseases leading to the demise of the patients, their age, duration of disease, and interval between death and autopsy are listed in Table I. [1]In the patient, MS 1, the lesions were almost entirely limited to the

Table I

Autopsy No.	*Age*	*Sex*	*Disease*	*Duration of disease*	*Hours death to autopsy*
3560	60	F	Cardiac aneurysm	1 yr.	4
3628	59	M	Pulmonary carcinoma; arteriosclerosis; well nourished	3 mo.	16
3838	63	M	Arteriosclerosis; cardiac mural thrombus; emaciated	9 mo.	8
3927	52	M	Pulmonary carcinoma; well nourished	4 mo.	6½
3752	69	M	Lymphosarcoma; diabetes; well nourished	4 mo. 7 yrs.	2
3730	66	M	Pulmonary carcinoma; emaciated	11 mo.	5
3873	65	M	Fibrosis and atrophy of pancreas; cirrhosis of liver; bronchial asthma; emaciated.	8 yrs. 25 yrs.	24
3687	57	M	Amyotrophic lateral sclerosis; well nourished	3 yrs.	17½
3546	64	F	MS of spinal cord; well nourished	7 yrs.	9½
3842	40	M	MS; chronic pyelonephritis; under-nourished	12 yrs.	5

spinal cord. The patient died of respiratory failure. The onset of the disease in patient MS 2 occurred fourteen years before death. The brains of 2 patients with extracranial malignant tumours (A–3730 and A–3752) and 1 with malnutrition, all free of demyelination, were also analysed. Except for terminal confusional psychosis of Case 3730, these 3 patients were clinically free of cerebral symptoms.

The brains were frozen at −15° and kept at this temperature without fixation for one to several days, when extraction suitably could be started. A control experiment

[1]We are indebted to Dr. N. Malamud, University of California School of Medicine, San Francisco, for kindly reviewing the neuropathology of these cases.

XUM

where repeated extractions were carried out on the same brain at various intervals of freezing was done. There was no loss of highly unsaturated lipids during storage.

Cortex and white matter were separated by careful dissection. In MS Case 2, a careful attempt was made to dissect out plaques from the surrounding white matter (designated as "lesions") although it is recognized that complete separation from normal tissue cannot be obtained by gross dissection. After homogenization in a Waring blender, one weighed aliquot (for lipid determinations) was re-homogenized and extracted according to Folch *et al.* (1951), another used for aquametry (Mitchell and Smith, 1948). Exposure to light was avoided wherever feasible. Extracts were kept under N_2. For estimating completeness of extraction, the residue in two instances was refluxed with Folch's mixture for twenty-four hours. This furnished less than 1 per cent additional lipids. The crude extracts were brought to near dryness under reduced pressure on a rotating evaporator. When attempts were made to follow Folch's purification procedure, the "fluffy layer" (Sperry, 1955) could not be entirely separated by either Folch's *et al.* (1959) or Sperry's (1955) procedure. Also, the prolonged exposure of lipids to air in Folch's procedure at temperatures above zero was undesirable. The residue, therefore, was taken up in petrol ether:chloroform 6:1. The small amount of material insoluble in this solution was re-extracted after flushing with N_2 with Folch mixture, under reflux for one hour. This added 3·9 to 9 per cent PUFA in the instance of the white, and 6·9 to 15·5 per cent PUFA in that of the grey matter and corresponding amounts of phospholipids.

The final extract was made up to volume and aliquots taken as indicated. PUFA were estimated by the isomerization procedure of Herb and Riemenschneider (1953), employing blanks and observing the precautions as recommended by Holman (1957). Complete absorption curves were obtained, and the individual values calculated according to Hammond and Lundberg (1953), assuming that the C20 and C22 pentænes were present in equal amounts. Cholesterol was determined according to Sperry and Webb (1950) and lipid phosphorus (L–P) by the method of Harris and Popat (1954). Phospholipid values were calculated by multiplying L–P by a factor of 25. Plasmalogens were estimated by Wittenberg's *et al.* (1956) procedure.

Results

The data in Table II (grey matter) and Table III (white matter) reveal total phospholipid and cholesterol values for the control cases (3560,

Table II.—Lipid Content of Adult Brain—Grey Matter
(in grammes/100 grammes wet weight)

Autopsy No.	*Phospho-lipid*	*Cholesterol*		*Total PUFA*	*Water*
		Total	*Free*		
3560	4·93	1·40	1·40		75·6
3628	3·55	1·11	0·99		74·0
3838	3·73	1·07	1·07	·79	81·5
3927	4·11	1·25	1·23	·88	82·7
3752	3·21	·79	·79	·76	81·9
3730	2·34	1·02	·97	·63	83·0
3873	3·15	·98	·03	·59	72·4
3687 (*a*)	3·09	1·15	1·15	·78	
(*b*)	3·12	1·25	1·25	·70	85·2
3546 MS 1	2·91	1·07	1·07	·89	70·7
3842 MS 2	2·84	1·00	1·00	·69	66·0

TABLE III.—LIPID CONTENT OF ADULT BRAIN—WHITE MATTER
(in grammes/100 grammes wet weight)

Autopsy No.	*Phospho-lipid*	*Cholesterol*		*Total PUFA*	*Water*
		Total	*Free*		
3560	7·52	5·14	5·14		64·8
3628	6·24	3·58	3·58		73·4
3838	7·84	3·82	3·82	·85	71·3
3927	8·28	5·32	5·22	·84	71·0
3752	4·22	3·47	3·47	·73	69·4
3730 (*a*)	5·00	3·12	3·08	·73	65·1
(*b*)	5·52	3·28	3·20	·74	—
(*c*)	5·61	3·49	3·49	·73	—
3873	6·06	3·66	0·05	·55	65·2
3687 (*a*)	6·29	3·70	3·70	·81	
(*b*)	6·08	3·69	3·69	·78	67·6
3546 MS 1	4·59	2·30	2·30	·79	63·6
3842 MS 2	5·26	3·60	3·60	·56	57·9
Lesions	3·17			·79	

3628, 3838 and 3927) that are within the range given for "normals" (Rossiter, 1955). The phospholipid levels of the grey matter of A-3730 and of A-3873, and those of the white matter of A-3730 and of A-3752 are at the lower limit of normal or below. These were patients with pulmonary carcinoma, lymphosarcoma and malnutrition (*see* Table I). The cholesterol was practically all unesterified, as found by Cumings (1953). Representative UV absorption curves on isomerized lipids of grey and white matter (A-3838) are illustrated in fig. 1. These compare well to those obtained on pure PUFA by Holman (1957) and to those by Klenk and Lindlar (1955) on purified brain phospholipids, and indicate that interfering substances were not present. The total PUFA varied from 0·80 to 0·93 grammes/100 grammes wet tissue for the grey, and 0·76 to 0·94 for the white matter in those cases where the phospholipids were within normal range. In the two tumour cases with phospholipid depletion, the total PUFA values were at the lower level of the other cases, or below (grey matter of A-3730). The lowest values for PUFA were seen in the case of malnutrition (A-3873).

Grey and white matter show a marked difference in the distribution of the individual PUFA (Tables IV and V). The hexænes predominate in the grey, the tetrænes in the white matter. Most of the trienes are located in the white matter; there are less dienes in the grey than in the white matter. It is also noteworthy that the brains removed at longer intervals after death (*see* Table I) showed no appreciable difference in their content of highly unsaturated fatty acids from those obtained soon after the demise of the patient.

In the 2 cases with disseminated MS, the phospholipids of both grey and white matter were at the lowest range of normal or below that. It

Fig. 1 ABSORPTION CURVES OF LIPIDS IN HUMAN BRAIN

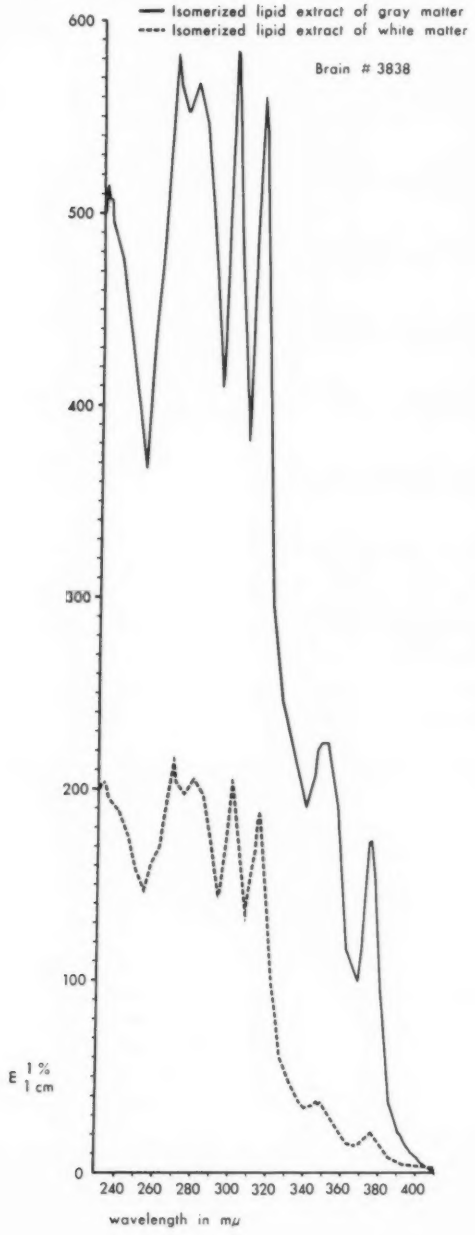


TABLE IV.—COMPOSITION OF POLYENES IN BRAIN—GREY MATTER
(in per cent of Total PUFA)

Autopsy No.	*Hexæne*	*Pentæne*	*Tetræne*	*Triene*	*Diene*
3838	46·5	·75	41·8	·72	3·3
3927	41·1	9·6	39·8	4·10	5·3
3752	52·6	9·6	35·4	·9	1·4
3730	56·4	6·9	31·6	0	5·0
3873	48·7	9·0	35·8	4·0	2·5
3687 (*a*)	55·3	7·3	33·1	0	4·2
(*b*)	49·0	7·1	37·3	1·9	4·3
3546 MS 1	56·5	9·0	30·6	0	3·8
3842 MS 2	50·0	10·5	39·5	·50	0·1

TABLE V.—COMPOSITION OF POLYENES IN BRAIN—WHITE MATTER
(in per cent of Total PUFA)

Autopsy No.	*Hexæne*	*Pentæne*	*Tetræne*	*Triene*	*Diene*
3838	16·4	6·8	54·5	12·2	10·2
3927	12·2	7·0	43·5	21·7	15·7
3752	18·8	8·4	48·9	13·8	10·1
3730 (*a*)	24·0	6·0	41·9	20·0	7·9
(*b*)	27·1	4·2	45·8	16·7	6·2
(*c*)	28·8	4·4	43·1	11·1	12·4
3873	13·6	7·7	49·8	16·9	12·0
3687 (*a*)	28·3	6·8	46·3	7·6	11·0
(*b*)	27·2	5·8	48·8	10·8	6·7
3546 MS 1	32·8	8·1	42·7	6·3	10·1
3842 MS 2	14·9	7·3	55·0	14·1	8·8
Lesions	37·2	7·8	44·9	6·3	3·7

TABLE VI.—PLASMALOGEN CONTENT OF HUMAN BRAIN TISSUE
(per 100 grammes wet weight)

Autopsy No.	*Lipid phosphorus in mm*	*Plasmalogen in mm*	*Plasmalogen/lipid phosphorus ratio*
	GREY MATTER		
3838	4·58	·986	·215
3927	5·03	·956	·190
3873	3·39	·693	·204
3842 MS 2	3·68	·627	·170
	WHITE MATTER		
3838	9·48	3·706	·391
3927	10·47	3·361	·321
3873 (*a*)	7·80	3·029	·388
(*b*)		2·861	·367
3842 MS 2	6·77	2·404	·355
Lesions	4·09	·281	·069

XUM

should be noted that in MS Case 1 the chemical analyses were done on tissue histologically free of lesions. Tissue consisting mainly of plaques (MS 2) showed marked depletion of the phospholipids.

The percentage of trienes in the white matter of MS Case 1, those of the lesions of MS 2 as well as in the case of amyotrophic lateral sclerosis were substantially less than those in the control brains.

Determination of plasmalogens was included only in the latter part of this investigation. The plasmalogen values and the plasmalogen/lipid phosphorus (Pl/LP) ratio for the control cases (A-3838 and A-3927) (*see* Table VI) are similar to those given by Rapport and Lerner (1959) for two cases. The case of malnutrition (A-3873) shows moderately lower levels, though the Pl/LP ratio is maintained, indicating that depletion of these two groups of lipids was similar in extent. Both the grey and white matter of MS Case 2 show an appreciably lower concentration, and in the plaque material there was a striking depletion of plasmalogens.

Variation of lipid content in different parts of the white matter was investigated by extraction of three different portions of brain tissue on A-3730. As may be seen from Table V (A-3730 A, B, C), the hexænes, tetrænes and dienes of the white matter are similar and only the triene shows a slight variation.

Discussion

Three aspects of these results invite comment: The distribution and levels of PUFA; the depletion of brain lipids in patients with other than CNS diseases, and the findings in the MS cases.

Klenk and Debuch (1959) in their extensive studies have reported a great array of highly unsaturated fatty acids of varying chain length as components of brain. Determinations of such complexity and detail were beyond the scope of this investigation.

The preliminary finding of a high hexæne content of the human cortex (Blancher *et al.*, 1952) has been corroborated by these determinations. The tetrænes present in large amounts in both grey and white matter may be allocated to the mitochondria and microsomes. These subcellular structures have been reported to be rich in tetrænes (Clement *et al.*, 1956; Mac Farlane *et al.*, 1960).

The depletion of phospholipids and of PUFA in brains of tumour patients free of cerebral metastasis is of particular interest when considered in conjunction with the demyelinating and degenerative changes occurring in such patients (Brain *et al.*, 1951; Åström *et al.*, 1958) and the hypotheses advanced as to their causative relationship to the tumour (Sinclair, 1958; Cavanagh *et al.*, 1959).

Phospholipid depletion occurring without discernible demyelination is not a novel observation. It has been reported for areas of MS brains free of lesions (Cumings, 1953) as well as for the early stage of experimental Wallerian degeneration (Majno and Karnovsky, 1958). It would

be reasonable to assume that it represents a pre-demyelinating "biochemical lesion" in both the tumour and the MS patient, though the mechanism leading to it may be and probably is a different one.

In the tumour patient, phospholipid depletion of the CNS like that observed in the organs of animals with experimental tumours (Boyd and Millar, 1959) may be due to competition for them or their components by the rapidly multiplying neoplastic cells. High concentration of phospholipids in malignant tumours has been reported (Stern and Willheim, 1943). It is further interesting that the PUFA level and PUFA/phospholipid ratio were lowered only in the tumour case associated with inanition (A-3730) and in the case of malnutrition, whereas, in the other tumour cases, significant differences of the PUFA values were not observed. This finding may possibly bear some relationship to Sinclair's (1958) surmise that changes in the CNS could raise from the association of malignancy with a subclinical PUFA deficiency.

The processes leading to reduced concentration of phospholipids in MS are even more obscure. It may be pertinent to note here that the trienes levels in the two MS cases and in a case of sudanophilic diffuse sclerosis to be reported elsewhere were significantly lowered. It is suggested that this may indicate altered enzyme activity. Holman and Widmer (1959) reported that the concentration of trienes in the cytochrome oxidase fraction of beef heart extracts was two to three times that in other enzymes and other subcellular fractions, thus linking trienes to cytochrome oxidase activity. Cytochrome oxidases are essential for the oxidative generation of adenosinetriphosphate, which, in turn, is needed for the synthesis of phospholipids (Kornberg and Pricer, 1953; Kennedy, 1959).

The transition from inadequate phospholipid concentration to visible demyelination and functional disturbance may be brought about through the essential role played by phospholipids in the formation of the mitochondrial membrane. This surmise is based on the pre-demyelinating removal of phospholipids in the very early stage of Wallerian degeneration (Majno and Karnovsky, 1958) when the periodic layers of myelin appear still intact but the axoplasm and mitochondria already reveal damage (Terry and Harkin, 1959).

Summary

(1) Polyunsaturated fatty acid concentrations for grey and white matter of human brain have been determined. The hexænes predominate in the grey, the tetrænes in the white matter. Most of the trienes are found in the white matter.

(2) In two brains of patients with extracranial tumours, depletion of phospholipids, and in one of them low levels of PUFA were noted. In histologically normal appearing areas of both the grey and white matter

XUM

of the brains of MS patients, the quantity of total phospholipids was reduced. There was decrease of plasmalogens proportional to the depletion of total phospholipids except in the MS plaques where the plasmalogens were only one-tenth of that in the controls.

(3) In the white matter of brains with primary demyelinating disease, the proportion of trienes was considerably lower than in all other brains examined. There was no other evidence of essential fatty acid deficiency in the two MS brains.

(4) In a case of severe malnutrition due to atrophy and lipomatosis of pancreas, the phospholipids were slightly, the PUFA strikingly depleted.

(5) It is suggested that depletion of phospholipids represents a chemical lesion occurring in both multiple sclerosis and in patients with extracranial tumours or nutritional deficiencies. Histologically evident demyelination is associated with additional chemical alterations, one of which is extensive removal of plasmalogens. A possible chemical pathway by which the former progresses to the latter has been discussed.

REFERENCES

Åström, K. E., Mancall, E. L., and Richardson, E. P., Jr. (1958) *Brain*, **81,** 93.

Blancher, G., Le Breton, E., and May, P. (1952) *C. R. Soc. Biol., Paris*, **146,** 219.

Boyd, E. M., and Millar, I. E. (1959) *Canad. J. Biochem.*, **37,** 1447.

Brain, W. R., Daniel, P. M., and Greenfield, J. G. (1951) *J. Neurol. Neurosurg. Psychiat.*, **14,** 59.

Brante, G. (1949) *Acta physiol. scand.*, **18,** suppl. 63.

Cavanagh, J. B., Greenbaum, D., Marshall, A. H. E., and Rubinstein L. J. (1959) *Lancet*, **2,** 524.

Clement, G., Clement, J., and Le Breton, E. (1956) *In* G. Popjak and E. Le Breton's "Biochemical Problems of Lipids." London, p. 385.

Cumings, J. N. (1953) *Brain*, **76,** 551.

—— (1955) *Brain*, **78,** 554.

Folch, J., Ascoli, I., Lees, M., Meath, J. A., and LeBaron, F. N. (1951) *J. biol. Chem.*, **191,** 833.

——, Webster, G. R., and Lees, M. (1959) *Fed. Proc.*, **18,** 228.

Gerstl, B., Davis, W. E., Jr., Smith, J. K., Athineos, E., and Herold, G. (1959) *Proc. Soc. exp. Biol., N.Y.*, **100,** 534.

Hammond, E. G., and Lundberg, W. O. (1953) *J. Amer. Oil Chem. Soc.*, **30,** 433.

Harris, W. D., and Popat, P. (1954) *J. Amer. Oil Chem. Soc.*, **31,** 124.

Herb, S. F., and Riemenschneider, R. W. (1953) *Analyt. Chem.*, **25,** 953.

Holman, R. T. (1957) *In* D. Glick's "Methods of Biochemical Analysis." New York, **4,** 99.

——, and Widmer, C. (1959) *J. biol. Chem.*, **234,** 2269.

Kennedy, E. P. (1959) *In* S. R. Korey's "The Biology of Myelin." New York, p. 260.

Klenk, E., and Debuch, H. (1959) *Ann. Rev. Biochem.*, **28,** 39.

——, and Lindlar, F. (1955) *Hoppe-Seyl. Z.*, **299,** 74.

——, and Montag, W. (1958) *J. Neurochem.*, **2,** 233.

Kornberg, A., and Pricer, W. E., Jr. (1953) *J. biol. Chem.*, **204,** 329.

Kurland, L. T., Mulder, D. W., and Westlund, K. B. (1955) *New Engl. J. Med.*, **252,** 649 and 697.

MAC FARLANE, M. G., GRAY, G. M., and WHEELDON, L. W. (1960) *Biochem. J.*, **74,** 43P.

MAJNO, G., and KARNOVSKY, M. L. (1958) *J. exp. Med.*, **108,** 197.

MILLER, H., and SCHAPIRA, K. (1959) *Brit. med. J.*, **1,** 737 and 811.

MITCHELL, J., Jr., and SMITH, D. M. (1948) "Aquametry." New York.

O'CONNOR, J. S., DAVIS, R. L., LANGWORTHY, O. R., and CHOW, B. F. (1960) *Proc. Soc. exp. Biol., N.Y.*, **103,** 180.

PLUM, C. M., and HANSEN, S. E. (1960) *Acta psychiat. neurol. scand.*, Suppl. 141, p. 84.

RAPPORT, M. M., and LERNER, B. (1959) *Biochim. biophys. Acta*, **33,** 319.

ROSSITER, R. J. (1955) *In* K. A. C. Elliott, I. H. Page and J. H. Quastel's "Neurochemistry." Springfield, Ill., p. 11.

SINCLAIR, H. M. (1958) International Conference on Biochemical Problems of Lipids: "Essential Fatty Acids." London.

SMITH, J. K., GERSTL, B., DAVIS, W. E., and ORTH, D. L. (1956) *A.M.A. Arch. Neurol. Psychiat.*, **76,** 608.

SOBOTKA, H., CHRISTOFF, N., and BAKER, H. (1958) *Proc. Soc. exp. Biol., N.Y.*, **98,** 534.

SPERRY, W. M. (1955) *In* D. Glick's "Methods of Biochemical Analysis." New York, **2,** 93.

——, and WEBB, M. (1950) *J. biol. Chem.*, **187,** 97.

STERN, K., and WILLHEIM, R. (1943) "The Biochemistry of Malignant Tumors." New York, p. 139.

TERRY, R. D., and HARKIN, J. C. (1959) *In* S. R. Korey's "The Biology of Myelin." New York.

THOMPSON, R. H. S. (1959) *In* J. N. Cumings and M. Kremer's "Biochemical Aspects of Neurological Disorders." Springfield, Ill., p. 35.

WITTENBERG, J. B., KOREY, S. R., and SWENSON, F. H. (1956) *J. biol. Chem.*, **219,** 39.

CHOLESTEROL METABOLISM AND THE BLOOD-BRAIN BARRIER: AN EXPERIMENTAL STUDY WITH 2-C^{14}-SODIUM ACETATE

BY

HAROLD J. NICHOLAS AND BYRON E. THOMAS

WHEN deuterium-labelled water or acetic acid was presented to adult rats (Waelsch, Sperry and Stoyanoff, 1940*a*; Bloch, 1950) little or no deuterium was found in cholesterol isolated from the brains of these animals. In addition, it has been the uniform experience of investigators studying cholesterol metabolism that adult brain reluctantly, if at all, incorporates steroid precursors into adult brain cholesterol *in vitro* (Srere *et al.*, 1950; Azarnoff, Curran and Williamson, 1958). In contrast, new born and young brain readily incorporated labelled precursors into the cholesterol molecule *in vitro* (Srere *et al.*, 1950) or *in vivo* (Waelsch, Sperry and Stoyanoff, 1940*b*). Based on this type of experimentation it has been concluded that as an animal reaches maturity the brain loses or almost completely loses its capacity to metabolize cholesterol. Recently, however, two different laboratories have shown that when C^{14}-labelled sodium acetate or 2-C^{14}- sodium mevalonate was injected intracerebrally (Nicholas and Thomas, 1959*a*, *b*) or intracisternally (McMillan, Douglas and Mortensen, 1957) into adult rats, presumably by-passing the blood-brain barrier, considerable C^{14} was found in brain cholesterol. A complete evaluation of these various data cannot be made at this time. A reasonable interpretation of the intracerebral data, however, would appear to be that adult rat brain tissue does possess an inherent capacity to synthesize cholesterol[1] but that this capacity is inhibited or held in check by factors at present largely unknown. By inference with a vast amount of information in adjacent areas of study (Bakay, 1956) the blood-brain-barrier seems a logical choice as one of the controlling factors. On this account it has seemed pertinent to investigate in more detail the effect of the blood-brain-barrier on brain cholesterol metabolism

[1]It should be recalled that *in vitro* experiments do not measure "turnover," and that unless one assumes a net increase of cholesterol during a short period following intracerebral injection of the precursors, some concurrent turnover of cholesterol must have occurred during this short period. It seems premature to discuss this point in more detail at this time.

since this "barrier" may control not only the influx of cholesterol precursors to the brain but the metabolism of cholesterol within the brain as well.

Several aspects related to this problem were investigated for this manuscript. First, if sodium acetate does not penetrate into the adult brain as a result of the barrier, then where the barrier is non-existent or of limited effect (as in fœtal or very young rats) acetate should penetrate into the brain and become incorporated into the cholesterol molecule. Strangely enough, there is no information in the literature on this question. Secondly, since the adult brain seems reluctant to incorporate acetic acid given parenterally or *in vitro* but does so when the precursor is injected directly into the brain, it has occurred to us that the cholesterol biosynthesis demonstrated by intracerebral injection may not be a true tissue biosynthesis but rather the result of secondary reactions occurring because of the brain wound. Tissue reactions in response to stab wounds have been explored in some detail (Macklin and Macklin, 1920; Hess, 1955*a*). The effect of a massive dose of labelled sodium acetate injected intraperitoneally into a normal adult rat was investigated also. The rationale for this experiment was the possibility that competition of other tissue sources (e.g. the liver) for the acetate may limit the amount of acetate reaching the brain when injected systemically. Lastly, while this work was in progress some observations on mouse brain cholesterol metabolism appeared (Kabara and Okita, 1959) and we have added our own observations obtained on this species.

Materials and Methods

$C^{14}H_3COONa$ was used as the cholesterol precursor in these experiments. It had a specific activity of 6·02 mc/mM and was purchased from Isotopes Specialties, Inc., Burbank, California. Intracerebral injections were performed as previously described (Nicholas and Thomas, 1959*a*). Rats and mice were of the Sprague-Dawley and CFW strain respectively, and guinea-pigs were purchased from a local dealer. All animals were sacrificed by decapitation. Where cholesterol concentration was to be determined, livers and brains were rinsed in distilled water and dried to constant weight *in vacuo*. The dried tissue was then saponified and the non-saponifiable fraction (obtained as previously outlined: Nicholas and Thomas, 1959*a*) was dissolved quantitatively in acetone-absolute ethanol (1:1). Duplicate or triplicate aliquots were then taken for cholesterol determination according to the Sperry-Webb procedure (Sperry and Webb, 1950). The remaining solution was used to obtain cholesterol digitonide, which was plated and counted for C^{14} activity according to earlier description (Nicholas and Thomas, 1959*a*). Fatty acids, where investigated, were also obtained and counted as previously described. The digitonides were not further treated, since it has been our experience with *in vivo* work of this nature that counts obtained on brain cholesterol digitonides correlate well with counts obtained from corresponding samples converted to the dibromides via the free sterol (i.e., the radioactivity in the digitonides is due largely to C^{14}–labelled cholesterol). In some of the experiments free cholesterol was obtained from the digitonide by the pyridine method and counted directly, after plating on 2·5 cm. diameter nickel planchets at a thickness of 1 mg. per planchet. Where a crude non-saponifiable fraction was investigated the material was similarly plated at 1 mg. per planchet. In those experiments in which a crude squalene fraction was investigated the general chromatographic separation of Langdon and Bloch (1953) was

used, the squalene being removed from Fisher chromatographic grade alumina (80–200 mesh) with petroleum ether (b.p. 30–60°), and a crude cholesterol fraction subsequently eluted with acetone-ethyl ether (1:1).

A pregnant rat and guinea-pig respectively were each injected with $5{\cdot}0 \times 10^7$ c.p.m. of $C^{14}H_3COONa$ several days pefore parturition. The rat delivered one young three days later (found on entering the laboratory in the morning) and was thereupon sacrificed under ether anæsthesia. Four more rats were removed *in utero* and sacrificed immediately. The pregnant guinea-pig was sacrificed twenty-four hours after injection with three hairless guinea-pigs removed *in utero*.

Two six-month-old female rats were subjected to intracerebral injection of 0·1 ml. of distilled water only, into the left cerebral hemisphere. Each rat thereupon received $1{\cdot}0 \times 10^7$ c.p.m. of $C^{14}H_3COONa$ intraperitoneally within ten minutes; they were sacrificed two hours after injection of the acetate. The brain was immediately removed and saponified; free cholesterol was obtained through the digitonide and counted directly. Fatty acids were also obtained and counted. In another series, 4 discarded breeder rats were similarly injected intracerebrally with 0·1 ml. of distilled water. Ten minutes later each was injected intraperitoneally with $4{\cdot}4 \times 10^7$ c.p.m. $C^{14}H_3COONa$. They were subsequently sacrificed at intervals of ten and twenty minutes, and one and three hours respectively. The brains were immediately saponified and non-saponifiable and fatty acid fractions obtained.

To determine whether a rather large dose of intraperitoneally administered sodium acetate would more effectively penetrate brain tissue a 340 gramme discarded breeder rat was injected intraperitoneally with $C^{14}H_3COONa$ at a dosage of 500 microcuries per kilogram of weight. Sacrifice was made ten minutes later, at which time the liver and brain were immediately saponified. Crude squalene and cholesterol fractions were obtained as described by Nicholas and Thomas (1959*b*) and fatty acids as described previously.

TABLE I.—INCORPORATION OF $C^{14}H_3COONa$ INTO CHOLESTEROL OF IMMATURE RATS; INTRACEREBRAL VS INTRAPERITONEAL INJECTION*

			Cholesterol specific activity†		
	Time sacrificed after		*Brain*		*Liver*
Rat No.	*injection (hrs.)*	*c.p.m. per mg.*	*c.p.m. per mg. chol. per gramme dried tissue*	*c.p.m. per mg.*	*c.p.m. per mg. chol. per gramme dried tissue*
1	2	763	22,890	105	1,124
2	2	680	18,000	—	—
3	2	128	3,878	92	902
4	2	111	3,430	274	2,713
5	4	119	3,737	—	—
6	4	67	2,050	134	1,541
7	4	129	4,154	—	—
8	6	172	5,470	—	—
9	6	172	3,732	—	—
10	6	99	3,523	—	—
11	24	171	6,047	—	—
12	24	121	5,265	—	—

*All rats were ten days old and weighed 20–23 grammes. Each received $5{\cdot}0 \times 10^6$ c.p.m. $C^{14}H_3COONa$, rats No. 1 and 2 by intracerebral injection, the others intraperitoneally.

†Calculated from infinitely thick samples of cholesterol digitonide.

Results

The blood-brain barrier present in fœtal and young guinea-pigs (Hess, 1955*b*) and more recently shown to be present for some dyes even in neonatal and very young rats (Millen and Hess, 1958) was not effective against sodium acetate in tracer doses. Labelled acetate given intraperitoneally to immature rats and guinea-pigs (Tables I and II) was found

Table II.—Incorporation of $CH^{14}C_3OONa$ Into Newborn and Young Guinea-pigs; Intracerebral vs Intraperitoneal Injection*

			Cholesterol specific activity†		
		Brain		*Liver*	
Guinea-pig No.	*Time sacrificed after injection (hrs.)*	*c.p.m. per mg.*	*c.p.m. per mg. chol. per gramme dried tissue*	*c.p.m. per mg.*	*c.p.m. per mg. chol. per gramme dried tissue*
1	5	20	1,052	27	114
2	5	9	424	22	109
3	5	12	595	28	117
4	2	1	68	1	7
5	2	1	27	4	51
6	5	6	284	3	36
7	5	5	207	2	25
8	24	9	410	8	109
9	24	6	275	9	120
10	2	56	2,498	3	32
11	2	60	2,870	2	28

*Guinea-pigs 1–3 were newborn (less than 1 day old) and weighed 66–80 grammes. Pigs 4–11 were ten days old and weighed 120–150 grammes. Each received $5{\cdot}0 \times 10^6$ c.p.m. $C^{14}H_3COONa$, pigs 1–9 intraperitoneally, pigs 10 and 11 intracerebrally.

†Calculated from infinitely thick samples of cholesterol digitonide.

in the brain in amounts comparable to that in the liver, indicating that the label penetrated freely into the brain tissue. In keeping with our previous work, even a massive dose of C^{14} acetate injected into an *adult* rat resulted in little incorporation of C^{14} into the lipides investigated (Table III); it

Table III.—Incorporation of C^{14} Into Adult Rat Lipids Following Intraperitoneal Injection of a Large Dose of $C^{14}H_3COONa$*

	Crude squalene Fraction	*Crude cholesterol fraction*	*Fatty acid fraction*
Organ	*Total c.p.m.*†	*c.p.m. per mg.*‡	*c.p.m. per mg.*
Brain	120	4	15
Liver	163,910	28,534	6,292

*A large female rat received 500 μc/kg. of $C^{14}H_3COONa$ intraperitoneally; sacrificed ten minutes after injection.

†Total counts in non-saponifiable fraction removed from alumina by petroleum ether.

‡Specific activity of non-saponifiable material eluted from alumina with acetone-ethyl ether (1:1), after prior elution with petroleum ether.

seems unlikely at this time that incorporation of any merit occurred in any other brain constituents. It will be noted that the amount of incorporation into both liver and brain cholesterol of the young guinea-pigs (Table II) was considerably lower than that of rats of the same age (Table I), whether the acetate was given intraperitoneally or intracerebrally. Although it seems likely that this difference may be due to the disparity in weights between guinea-pigs and rats at any post-natal age, attention should be called to the work of Schwenk (Schwenk, Alexander and Fish, 1955). These investigators, referring to experiments with the guinea-pig, suggest that "evidently the reactions which convert acetate into cholesterol and this into other products are much slower than in the rat. The guinea-pig does not synthesize cholesterol as easily and it cannot cope with it as well as the rat." A low value of 21 c.p.m. per mg. of cholesterol from the mother guinea-pig liver twenty-four hours after injection of the acetate may substantiate these conclusions.

In both the rat and guinea-pig, sodium acetate injected intraperitoneally into the mother was incorporated into fœtal brain cholesterol (Table IV).

TABLE IV.—INCORPORATION OF C^{14} INTO FOETAL RAT AND GUINEA-PIG CHOLESTEROL FOLLOWING MATERNAL INJECTION OF $C^{14}H_3COONa$*

	Brain		*Liver*	
Rat No.	*c.p.m. per mg.*	*c.p.m. per mg. chol. per gramme dried tissue*	*c.p.m. per mg.*	*c.p.m. per mg. chol. per gramme dried tissue*
1	11	261	6	55
2	10	182	7	40
3	9	169	6	26
4	11	217	6	37
5	6	139	6	48
Guinea-pig No.				
1	9	213	3	11
2	9	232	5	17
3	9	212	3	5

*Rat No. 1 was newly born and was sacrificed when found. All other animals were removed *in utero* and sacrificed immediately. The rats weighed 10–12 grammes, the guinea-pigs 17–20 grammes. After removing aliquots from the non-saponifiable fractions for cholesterol determination, 2·0 mg. of carrier cholesterol was added to the rat and pig brain fractions and 4·0 mg. to the rat liver fractions. No correction is made for these dilutions. Values are reported as free cholesterol calculated from infinitely thick digitonide samples. Maternal rat and guinea-pig each received $5{\cdot}0 \times 10^7$ c.p.m. of $C^{14}H_3COONa$ intraperitoneally.

It will be noted, however, that the specific activity of the fœtal rat and guinea-pig brain cholesterols were not greatly different, and the liver values were not grossly discrepant in contrast to the data obtained with older animals. Whether this is related to the fact that the fœtal weights are approximately the same or to other factors (discussed by Schwenk) cannot

be answered at this time. Popják had previously shown that C^{14}-labelled acetate crossed the placental barrier and was incorporated into cholesterol of various tissues of the fœtus (Popják, 1954); fœtal brain was not investigated. While our results are not entirely surprising, based on the work of Popják, experimental verification seemed needed. In the fœtal rat and guinea-pig as well as the post-natal animals there seems to be little or no blood-brain barrier to sodium acetate.

In both the young rat and guinea-pig (Tables I and II) incorporation of acetate into brain cholesterol was more effective by the intracerebal than the intraperitoneal route. This is presumably due to the more ready availability of substrate to the brain when presented by intracerebral injection. It will be noted that the brain and liver cholesterol specific activities of the ten-day-old rats and guinea-pigs are approximately the same when expressed as c.p.m. per mg. of cholesterol. Thus the acetate is freely available to brain as well as liver in both rats and guinea-pigs of this age. Expressed as c.p.m. per mg. of cholesterol per gramme of tissue, however, the values for brain become proportionately higher than those of the liver in both species of animal, due to the higher concentration of cholesterol in brain than in liver. This factor should be considered in comparing the specific activities of brain and liver cholesterol in tracer experiments, since the total quantity of sterol in the respective organs differs by a factor of about ten. Data for the experiments in which 2–C^{14}-sodium acetate was injected intraperitoneally following intracerebral injection of water are shown on Table V. None of the rat brains examined contained more than a trace of C^{14} in the lipid fractions investigated, an amount corresponding to that found when an equivalent quantity of labelled acetate was given intraperitoneally to normal, unoperated rats. Simple wounding of the brain did not permit acetate from the systemic circulation to enter the brain

TABLE V.—INCORPORATION OF C^{14} INTO ADULT RAT BRAIN LIPIDS FOLLOWING INTRAPERITONEAL INJECTION OF $C^{14}H_3COONa$: EFFECT OF BRAIN WOUNDS*

Rat No.	*Time sacrificed (min.) after intraperitoneal injection*	*Specific Activity, c.p.m. per mg.* *Crude Non-saponifiable fraction*	*Crude cholesterol fraction†*	*Fatty acid fraction*
1	10	—	1	12
2	10	—	1	4
3	10	10	—	12
4	20	10	—	12
5	60	6	—	12
6	120	10	—	14

*Each rat received 0·1 ml. of distilled H_2O intracerebrally ten minutes prior to the intraperitoneal injection of $1{\cdot}0 \times 10^7$ c.p.m. of the labelled acetate.

†Counted as free cholesterol after conversion from the digitonide via the pyridine method.

through the wound area and become incorporated into the non-saponifiable material of the tissue. Therefore events coincident to the wounding (macrophage infiltration, etc., Macklin and Macklin, 1920) are not responsible for the cholesterol biosynthetic phenomenon.

Although only a few experiments were performed with adult mice, the results (Table VI) in general parallel our findings with adult rats; namely,

TABLE VI.—INCORPORATION OF C^{14} INTO MOUSE BRAIN AND LIVER CHOLESTEROL FOLLOWING INTRAPERITONEAL INJECTION OF $C^{14}H_3COONa$*

Mouse No.	*Time of Sacrifice (min.) after C^{14} injection*	*Specific activity of crude cholesterol, c.p.m. per mg.†*	
		Brain	*Liver*
1	5	3	—
2	10	4	26
3	15	4	—
4	20	8	175
5	30	7	211
6	60	9	25

*Each mouse received $1{\cdot}0 \times 10^7$ c.p.m. of $C^{14}H_3COONa$.

†Material in non-saponifiable fraction eluted from alumina with acetone-ethyl ether (1:1) after prior elution with petroleum ether.

little incorporation of C^{14}–labelled acetate into brain cholesterol when injected intraperitoneally as compared to the amount incorporated into liver cholesterol during the same period. Cholesterol-C^{14} values following intracerebral injection of C^{14}-acetate were disappointingly low (unpublished observations). This may reflect the difficulty in performing the injection of fluid properly into the brain area of such a small animal. Some interesting comments by Okita and Kabara (1959) will merit further investigation with this mammal. Other (unpublished) observations include the fact that, as with rat brain tissue, adult mouse, guinea-pig and hamster brain tissue does not incorporate C^{14}-labelled acetate into cholesterol *in vitro*.

DISCUSSION

At the present time there is no satisfactory biochemical explanation for the fact that under most experimental conditions cholesterol in the adult central nervous system appears metabolically inert. All observations on the rat, at least, are in agreement that "turnover" of cholesterol in the adult brain must be limited, if not negligible, and the implications from these observations are that adult brain tissue has lost its ability to metabolize cholesterol. Yet such a conclusion cannot be entirely valid if one considers the recent experiments from our own laboratory which demonstrate active cholesterol biosynthesis from both acetate and mevalonic acid when these precursors are injected into the intact brain. Again, considering only synthetic capacity, it appears more than circumstantial that squalene is present in adult brain, and that the enzyme isopentenyl pyrophosphate

isomerase, so intimitely connected with cholesterol biosynthesis, should also be present in adult brain tissue (Agranoff, Eggerer, Henning and Lynen, 1960). The question then arises, is the "block" in cholesterol metabolism of adult brain due to inability of the tissue to further metabolize cholesterol synthesized by the organ rather than inability of the tissue to synthesize the sterol? Opposing this is the fact that one cannot demonstrate cholesterol biosynthesis in the test tube with any number of adult brain tissue preparations. In considering the latter phenomenon it should be borne in mind that brain as well as other tissue frequently does not perform *in vitro* as expected, and that with respect to cholesterol biosynthesis *in vitro*, adult brain tissues and adipose tissue have much in common. The latter tissue also apparently cannot synthesize cholesterol *in vitro* (Feller, 1954).

In conclusion, the one factor which can at present be established as definitely influencing adult brain cholesterol metabolism—in the broadest sense—is the blood-brain barrier. Other than by prohibiting the entrance of cholesterol precursors to the adult brain, the specific influence of this barrier remains unknown. It appears that we have only scratched the surface in our knowledge of cholesterol metabolism in the central nervous system.

Summary

The blood-brain barrier present for certain dyes in immature rats and guinea-pigs was not effective for tracer doses of 2-C^{14}-sodium acetate since intraperitoneally administered acetate became incorporated into brain cholesterol of these animals as well as into liver cholesterol. When administered to a pregnant rat and guinea-pig respectively, the C^{14}–label crossed the placental barrier, as expected, and became incorporated into fœtal brain cholesterol. Even a massive dose of C^{14}–labelled acetate given intraperitoneally to an *adult* rat produced no marked labelling of the brain lipids investigated. From sham intracerebral injection experiments it was concluded that the incorporation of cholesterol precursors into adult brain cholesterol following intracerebral injection of the precursors is not the result of secondary effects of the brain wound *per se*. Factors affecting cholesterol metabolism in the adult brain are discussed.

Acknowledgment

We wish to thank Mrs. Kathryn Smith for technical assistance during this study, which was supported by a grant from the National Science Foundation.

References

Agranoff, B. W., Eggerer, H., Henning, U., and Lynen, F. (1960) *J. biol. Chem.*, **235**, 326

Azarnoff, D. L., Curran, G. L., and Williamson, W. P. (1958) *J. Natl. Cancer Inst.*, **21**, 1109.

Bakay, L. (1956) "The Blood-Brain Barrier." Springfield, Ill.

BLOCH, K. (1950) *In* "A Symposium on Steroid Hormones." Edited by E. S. Gordon, Lancaster, Pennsylvania, p. 33.
FELLER, D. D. (1954) *J. biol. Chem.*, **206,** 171.
HESS, A. (1955*a*) *A.M.A. Arch. Neurol. Psychiat.*, **74,** 149.
—— (1955*b*) *J. comp. Neurol.*, **102,** 65.
KABARA, J. J., and OKITA, G. T. (1959) *Fed. Proc.*, **18,** 408.
LANGDON, R. G., and BLOCH, K. (1953) *J. biol. Chem.*, **200,** 135.
MACKLIN, C. C., and MACKLIN, M. T. (1920) *Arch. Neurol. Psychiat., Chicago*, **3,** 353.
MCMILLAN, P. J., DOUGLAS, G. W., and MORTENSEN, R. A. (1957) *Proc. Soc. exp. Biol., N.Y.*, **96,** 738.
MILLEN, J. W. and HESS, A. (1958) *Brain*, **81,** 248.
NICHOLAS, H. J., and THOMAS, B. E. (1959*a*) *J. Neurochem.*, **4,** 42.
——, —— (1959*b*) *Biochim. biophys. Acta*, **36,** 583.
POPJÁK, G. (1954) *Cold Spr. Harb. Symp. quant. Biol.*, **19,** 200.
SCHWENK, E., ALEXANDER, G. J., and FISH, C. A. (1955) *Arch. Biochem., Biophys.*, **58,** 37.
SPERRY, W. M., and WEBB, M. (1950) *J. biol. Chem.*, **187,** 97.
SRERE, P. A., CHAIKOFF, I. L., TREITMAN, S. S., and BURSTEIN, L. S. (1950) *J. biol. Chem.*, **182,** 629.
WAELSCH, H., SPERRY, W. M., and STOYANOFF, V. A. (1940*a*) *J. biol. Chem.*, **135,** 291.
——, ——, —— (1940*b*) *J. biol. Chem.*, **135,** 297.

ACTION OF A BARBITURATE DRUG (AMYLOBARBITONE SODIUM) ON THE VESTIBULO-OCULAR REFLEX

BY

C. RASHBASS AND G. F. M. RUSSELL

(From the Institute of Psychiatry, The Maudsley Hospital, London)

Two of the situations in which the eyes move smoothly are when the semicircular canals are stimulated and when a moving object in the field of view is tracked. A nystagmus is the result of repeated alternation of slow, smooth movements and jerky movements: it is termed vestibular if it results from stimulation of the semicircular canals, or optokinetic if it is the response to a succession of objects moving smoothly in the field of vision. When the semicircular canals are stimulated in a subject who is free to fixate his environment, the situation is complicated. As soon as the vestibular stimulus causes smooth deviation of the eyes—and therefore a movement relative to the environment—an optokinetic influence is superadded. Because the movement of the environment relative to the eyes is in the direction opposite to that of the eyes themselves, the superadded optokinetic stimulus tends to counteract the eye movement induced by the vestibular stimulus. The optokinetic influence can be avoided by keeping the subject in darkness or by having him close his eyes when an enhancement of the nystagmus would be expected. This effect has been demonstrated experimentally by Fenn and Hursh (1937) in the case of post-rotational nystagmus and by Perlman and Case (1939) with caloric induced nystagmus.

Another way of eliminating the smooth pursuit response of the eyes is by administering a barbiturate drug. In this way Bergman *et al.* (1952) abolished optokinetic nystagmus in subjects watching a rotating striped drum. Rashbass (1959) has suggested that this effect is due to interference with the mechanism for smooth movements which ordinarily ensures a stationary image on the retina. It may be supposed, therefore, in a subject tested with his eyes open, that one of the actions of a barbiturate drug on the vestibulo-ocular reflex would be to enhance the nystagmus in the same way as when conducting the experiment in darkness. On the other hand, Anderson *et al.* (1958) have described a direct effect of amylobarbitone sodium on the vestibular response: increasing doses resulted first in a

XUM

decrease in frequency of the nystagmus, and later in its abolition and replacement by the fine, rapid nystagmus on deviation of the eyes, which is characteristic of barbiturates.

The aim of the experiments reported in this article was twofold. First, it was proposed to test the hypothesis that a barbiturate drug would abolish the inhibiting effect of visual fixation on the vestibular nystagmus. Secondly, the direct action of the drug on the true vestibular response was investigated after the optokinetic effect had been avoided by testing the subjects in darkness.

METHODS

Caloric Stimulation

The vestibulo-ocular response to caloric stimulation was studied in two normal subjects (C. R. and G. R.). The following measures were taken to ensure that successive stimuli was comparable. The subject tested lay supine on a couch with his head tilted at 30 degrees above the horizontal plane by means of sandbags, so as to keep the lateral semicircular canal vertical. A polythene tube of 3 mm. bore was fixed to the external ear with sticking plaster and one end introduced into the external auditory meatus; in this way the nozzle of the tube was kept in constant relationship to the ear drum. The outer end of the polythene tube was attached to a length of rubber tubing connected to a water-containing canister placed four feet above the subject's head. The water was at room temperature (17° C.) to obviate the need for insulation against heat exchange. Water was poured into the ear for sixty seconds, the total flow amounting to about 500 ml.

Record of Eye Movements

A continuous pen record of the movements of the eyes was obtained by the method of AC-coupled electro-oculography; the time constant was 1 second. A rubber suction cup surface electrode (Shackel, 1958) was placed at each outer canthus thus detecting changes in potential due to lateral movements of the eyes; the earth electrode was placed on the forehead. Van Egmond *et al.* (1954) and Henriksson (1956) have demonstrated that the sensitivity of the semicircular canals is best indicated by the angular velocity of the eyes during the slow phase of the nystagmus and not by the duration of the nystagmus. The speed of the slow movement was measured by the sum of successive vertical displacements on the records per unit time, and was expressed in arbitary units. The record was sampled every twenty seconds and the value obtained was plotted against time from the onset of the irrigation (fig. 2).

Plan of Investigation

(1) A preliminary experiment was done in one subject (G. R.) whose caloric response was measured before and after an intravenous injection of

300 mm. sodium amytal (amylobarbitone sodium). The subject was asked to open and close his eyes alternately for ten-second periods. The drug was found to interfere with the subject's ability to track a pendulum swinging in the plane of his eyes: the smooth pursuit movement was replaced by a series of fixation jerks. Although thirty minutes were allowed between the two irrigations of the ear, it was suspected that this method did not allow for the decreased vestibular responsiveness after the first caloric stimulus. Accordingly, a series of experiments designed to eliminate this source of error was conducted on each subject.

(2) A control series of eight irrigations at fifteen-minute intervals was performed to assess the pattern of decreasing responsiveness of the vestibule without the drugs. On a subsequent day, the same procedure was gone through while sodium amytal was given in increasing amounts. It was thus possible to compare the pattern of response to repeated caloric stimulation with and without the drug. In the first subject (G. R.), 120 mg. sodium amytal was given orally just after the first irrigation, and was followed by 60 mg. every fifteen minutes until a total of 300 mg. had been given. The second subject (C. R.) was injected with 125 mg. sodium amytal intravenously before the third, fifth and seventh irrigations. Closure of the eyes as a means of preventing visual fixation in the preliminary experiment was replaced by plunging the room in total darkness and instructing the subject to keep his eyes open; it had been found that eye closure sometimes temporarily inhibited the nystagmus. Throughout the irrigation and for as long as the nystagmus was present (two to three minutes), the light was switched on and off alternately for periods of ten seconds.

RESULTS

Preliminary Experiment

Fig. 1 shows samples of records taken immediately after the end of irrigation when the ocular response was maximal. Before the intravenous injection of sodium amytal, the subject was able to track the swinging pendulum smoothly without any refixation jerks and opening the eyes completely abolished the vestibular nystagmus. After the injection of sodium amytal, smooth tracking of the pendulum was no longer possible and opening the eyes failed to inhibit the nystagmus. On the other hand, the drug did not appear to reduce the speed of the slow movement of the nystagmus.

Controlled Experiments

Fig. 2A illustrates the response curves to successive cold irrigations of the ear in subject C. R. before giving sodium amytal. In both subjects the speed of the slow movement was at its maximum near the end of the irrigation and diminished rapidly until it became no longer measurable 100 to 150 seconds later. The greatest response followed the first two

XUM

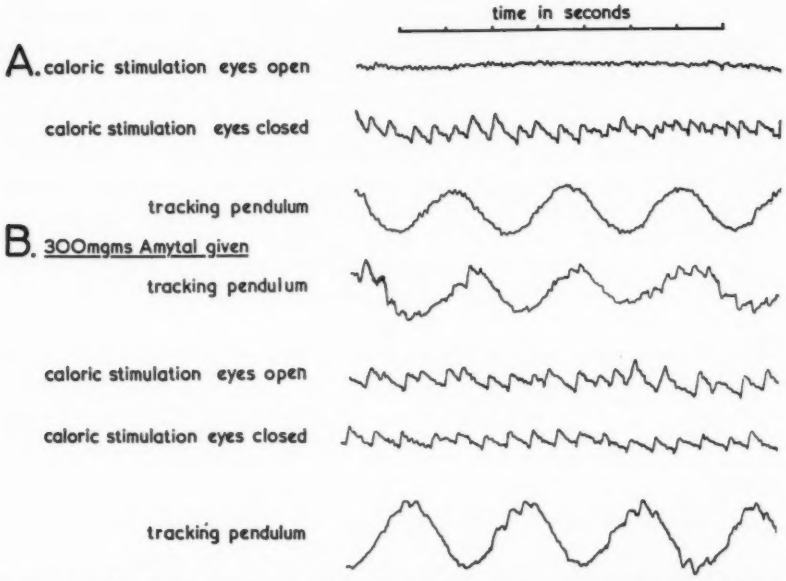


FIG. 1.—Vestibular nystagmus and ocular tracking of swinging pendulum in subject G. R. A. Before sodium amytal. Vestibular nystagmus was inhibited by opening the eyes. The subject was able to track the pendulum smoothly. B. After 300 mg. sodium amytal intravenously. Both at the beginning and the end of the experiment the pendulum was tracked in a series of interrupted jerks. Opening the eyes no longer inhibited vestibular nystagmus which was otherwise not materially influenced by the drug.

caloric stimulations; thereafter the responses were much reduced but remained at a more or less constant level and were chosen for comparison with the corresponding response curves after administration of sodium amytal.

The action of sodium amytal was studied separately on the nystagmus when the lights were switched on and in darkness (fig. 2B). When the lights were switched on there appeared a nystagmus which had not been apparent previously (the dotted lines in fig. 2); visual fixation no longer had its inhibiting effect on the nystagmus. In subject C. R., increasing doses of sodium amytal caused a progressive speeding up of the slow movement until the nystagmus present with the lights switched on approximated that in the dark. In subject G. R., who was given the drug orally, the inhibitory effect of visual fixation was diminished but to a lesser degree so that the speed of the slow movement when the lights were switched on never equalled that in darkness. The action of sodium amytal on the nystagmus in darkness was ascertained next. The speed of the slow

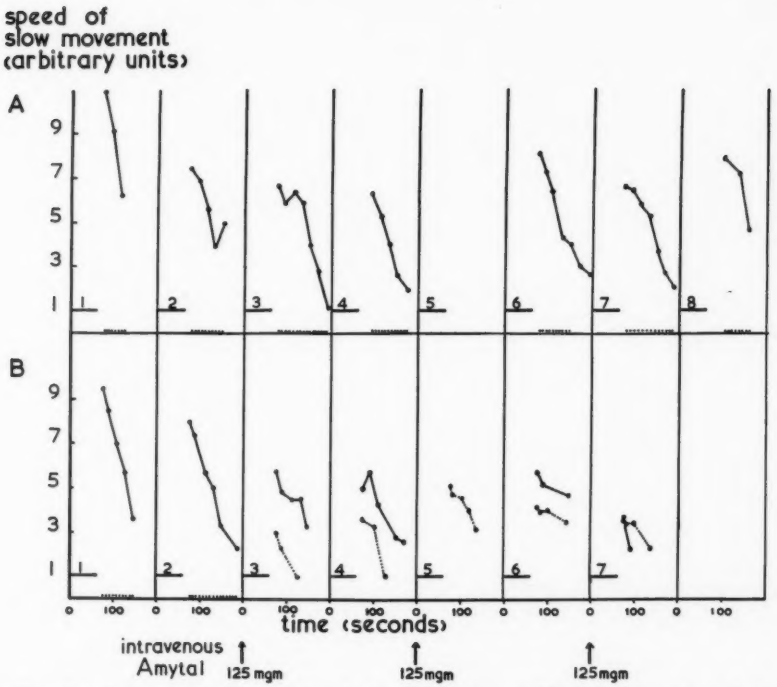


FIG. 2.—Responses to repeated caloric stimulation at fifteen-minute intervals in subject C. R. Full line shows speed of slow movement in darkness. Dotted line shows speed of slow movement when the lights were switched on. Period of caloric stimulation is marked and numbered. A. Before sodium amytal. No record was obtained during stimulation 5. B. Effect of sodium amytal. There was a progressive increase in the speed of the slow movement of the nystagmus when the lights were switched on. There was no significant reduction in the speed of the slow movement of the nystagmus in darkness. No record was obtained in darkness during stimulation 5.

movement at 75 and 125 seconds from the onset of irrigation was measured in both subjects before and after receiving the drug. The decrease in the speed of the slow movement that occurred spontaneously without sodium amytal was expressed as the difference between the values obtained after the first irrigation and those obtained after the third and subsequent irrigations. The decrease in the speed of the slow movement after sodium amytal was calculated in the same way. The results for each subject are shown in Table I. In subject C. R. the reduction in the speed of the slow movement was somewhat more marked after sodium amytal, but this effect was only small; in subject G. R. sodium amytal likewise had a small effect only, this time in the opposite direction. Analysis of variance showed that

XUM

TABLE I.—EFFECT OF SODIUM AMYTAL ON THE DECREASE IN THE SPEED OF THE SLOW MOVEMENT OF THE NYSTAGMUS IN DARKNESS (EXPRESSED IN ARBITRARY UNITS AS THE DIFFERENCE BETWEEN THE FIRST AND THE STATED CALORIC STIMULATIONS)

	Subject C. R.				*Subject G. R.*			
	At 75 sec.		*At 125 sec.*		*At 75 sec.*		*At 125 sec.*	
Caloric stimulation	*Without sodium amytal*	*With sodium amytal*	*Without sodium amytal*	*With sodium amytal*	*Without sodium amytal*	*With sodium amytal*	*Without sodium amytal*	*With sodium amytal*
3	4·1	3·6	0·1	1·2	4·9	3·5	4·1	2·4
4	4·5	4·5	1·9	2·0	4·2	3·7	4·2	2·7
5	—	—	—	—	4·5	3·5	3·5	4·3
6	2·8	3·8	1·6	0·9	4·0	3·2	4·9	4·0
7	4·1	5·8	0·8	3·0	3·9	2·8	3·1	2·9
Mean	3·88	4·43	1·10	1·78	4·30	3·50	3·96	3·26

these results were not statistically significant ($F=0{\cdot}19$; d.f.$=35$; $P>0{\cdot}05$).

In both subjects, the action of the drug on the nystagmus in darkness is negligible when compared to very definite interference with the inhibiting effect of visual fixation on the vestibular nystagmus.

DISCUSSION

The hypothesis formulated in the introduction has been supported by the experimental evidence. Sodium amytal abolishes the inhibiting effect of visual fixation on a vestibular nystagmus. After being given a moderate dose of the drug the subject may show the same amount of nystagmus as when the vestibular stimulation is carried out in darkness. It may be concluded that sodium amytal interferes with the mechanism for smooth movements which maintains a stationary image on the retina. In the case of nystagmus produced by vestibular stimulation, this mechanism normally prevents movement of the eyes relative to the environment: in interfering with it, the drug allows an unimpeded nystagmus in response to vestibular stimulation. This observation is the counterpart of the abolition by a barbiturate drug of the optokinetic nystagmus ordinarily elicited when a subject observes a rotating striped drum; in this instance it is the environment which can no longer be followed by the eyes.

The second purpose of the study was to determine the effect of sodium amytal on the vestibulo-ocular reflex itself, when the subject is tested in darkness and the complicating effects of visual fixation are eliminated. With the doses given, no convincing diminution of the uncomplicated vestibulo-ocular reflex was detected even though smooth pursuit movements had been abolished, as shown by the inability of the eyes to follow a swinging pendulum and the loss of the inhibiting effect of visual fixation of the nystagmus. This finding is in agreement with that of Dohlman *et al.* (1956) who observed no decrease in the speed of the slow phase of caloric nystagmus after an intravenous injection of Evipan. The work of

Anderson *et al.* (1958), which suggests a direct effect of amylobarbitone sodium on the vestibular reflex, cannot be compared easily because their experiments were insufficiently controlled.

It is evident that sodium amytal, to some extent, selectively interferes with the smooth pursuit movements of the eyes while the smooth movements resulting from vestibular stimulation are unaffected. This observation is of interest because it suggests that the reflex mechanisms controlling the two types of smooth eye movements are capable of pharmacological dissociation, even though they must share a considerable part of their anatomical pathways. The exact delineation of these pathways is uncertain as is also the site of action of barbiturate drugs. However, the present findings offer the hope that a deeper understanding of either problem may be used to shed light on the other.

Summary

A vestibular nystagmus was elicited in two normal subjects by cold caloric stimulation. The nystagmus was recorded by the method of electro-oculography. Allowance was made for the diminished response to repeated caloric stimulation.

Sodium amytal in moderate doses abolished the inhibiting effect of visual fixation on the nystagmus without significantly interfering with the vestibulo-ocular response itself.

It is concluded that this barbiturate drug selectively blocks the pathways responsible for the smooth pursuit movements of the eye without reducing reflex vestibular smooth movements.

Acknowledgment

We wish to thank Eli Lilly & Co. Ltd., for assisting the work with a research grant, and Dr. A. E. Maxwell for statistical advice.

REFERENCES

Anderson, P. J., Diamond, S. P., Bergman, P. S., and Nathanson, M. (1958) *Neurology*, **8**, 741.

Bergman, P. S., Nathanson, M., and Bender, M. B. (1952) *A.M.A. Arch. Neurol. Psychiat.*, **67**, 357.

Dohlman, G., Henriksson, N. G., and Andren, G. (1956) *Acta Oto-laryng. Stockh.*, **46**, 323.

Egmond, A. A. J. Van, and Tolk, J. (1954) *Acta Oto-laryng. Stockh.*, **44**, 589.

Fenn, W. O., and Hursh, J. B. (1937) *Amer. J. Physiol.*, **118**, 8.

Henriksson, N. G. (1956) *Acta Oto-laryng. Stockh.*, Supp. 125.

Perlman, H. B., and Case, T. J. (1939) *Laryngoscope, St. Louis.* **49**, 217.

Rashbass, C. (1959) *Nature, Lond.*, **183**, 897.

Shackel, B. (1958) *J. Appl. Physiol.*, **13**, 153.

XUM

NOTICES OF RECENT PUBLICATIONS

PSYCHIATRY

Experimental Studies of the Mode of Action of Electroconvulsive Therapy. Ed. JAN-OTTO OTTOSSON. 1960. Pp. 141. *Acta psychiat. neurol. Scand.* suppl. 145. No price stated.

This work by Ottosson, with the collaboration of Kirstein and Cronholm, comes from Stockholm: it is extremely well planned and carried out, and goes far to replace speculations about the mode of action of E.C.T. by facts.

Lidocaine (xylocain) injected intravenously before E.C.T. shortens and modifies the seizure EEG-pattern, reducing spike activity and shortening the postseizure silence. Comparisons were made between patients treated with lidocaine-modified seizures, and with seizures induced by liminal and by supraliminal stimulation. It was concluded that the depression-relieving activity of E.C.T. was due to seizure activity, as were the EEG changes after treatment, whereas the adverse effect on memory (in particular on retention) was most marked with supraliminal stimulation and was ascribed to effects of the current other than seizure activity.

Neurologists will be particularly interested in the account of modification of seizure activity by lidocaine, the residual activity resembling that of *petit mal*, and in the discussion it is suggested that "the build-up and spread of the residual and of the blocked activity may have different mechanisms, the former mainly being dependent on synaptic transmission, the latter on undifferentiated spread of excitation due to diffuse effects of electrical fields."

This book is a valuable addition to the Supplements, and should interest psychiatrists and neurologists alike.

RICHARD PRATT.

Chemotherapy in Emotional Disorders: The Psychotherapeutic Use of Somatic Treatments. By F. F. FLACH, M.D., and P. F. REGAN, M.D. 1960. Pp. 314. London: McGraw-Hill. Price £3 17s. 6d.

This book is concerned with the help that somatic treatments can give in mental illness. Psychotherapy, in particular psychoanalysis, is regarded as the best treatment, and measures such as E.C.T. and chlorpromazine are applied reluctantly, and their beneficial results then ascribed to their enabling the patient to assimilate the previous (unrewarding) psychotherapy. "She was placed in psychotherapeutic management for a period of six months in the hospital and successfully analysed her lifelong masculine drives . . . Her depression remained intense, however, and it was necessary to administer E.C.T. in the sixth month of hospitalization. The patient received seven E.C.T.s at this time and was completely relieved of depression. She remained in hospital two more months, applying the previously learned elements of psychodynamics, and had no recurrence of depression." Somatic treatments are given grudgingly, since "the suffering serves as a motivation to participate in psychotherapy." With such a theoretical background physical methods of treatment are applied in a half-hearted manner, and it is not surprising that optimal results are not obtained.

The danger of cardiovascular complications is held to outweigh the benefit in schizophrenia from the combination of E.C.T. and chlorpromazine. The use of lithium in mania and of progesterone in premenstrual tension is not mentioned. In the

discussion of leucotomy, it is stated that "it is difficult to discern any significant difference in the effectiveness of the various operative procedures," and "frequently they (post-leucotomy patients) will urinate in public or appear socially in states of undress."

This book is an interesting result of the impact of the newer drugs on a psychodynamically orientated psychiatry, but the challenge is not met squarely.

RICHARD PRATT.

Lehrbuch der Psychiatrie. EUGEN BLEULER. Tenth edition, revised by MANFRED BLEULER. Pp. 629. Berlin: Springer. Price 56 DM.

This is the tenth edition of Bleuler's classic "Textbook of Psychiatry" first published in 1916, and the fourth revision by his son and successor at Zurich (an English translation appeared in 1924). Although first published half a century ago it is due to Bleuler's original genius and the incorporation of new matter that the text remains up to date. With the exception of advice on neuropathology from Scheidegger, on electroencephalography from Hess, and sections on forensic psychiatry by colleagues in other German-speaking countries, the book is the work of one master mind and gives a balanced yet detailed account of modern psychiatry and its links with medicine in general and neurology in particular—the chapters on mental disturbances with brain disease such as tumour, injury and atrophy are exemplary.

It was Bleuler's intention to advance psychiatry—and for him psychotherapy was an integral part of it—by injecting Freud's dynamic psychological formulations and insights into the static descriptive Kraepelinian system of disease often artificially separated by symptomatology and clinical course. Unhappily these schools still regard themselves in opposition as if psychiatry were exclusively either a somatic or a psychological affair. How much it is enriched both for doctor and patient by combining both approaches emanates from every page of "Bleuler."

RICHARD HUNTER.

LOCAL EFFECTS OF BRAIN INJURY

Somato-sensory Changes after Penetrating Brain Wounds in Man. By J. SEMMES, S. WEINSTEIN, L. GHENT and H. L. TEUBER. Pp. 91. Oxford University Press. Price 32s.

This monograph should serve as a model for others on a complex subject of this kind. It is a cautious assessment of experimental findings within a series of carefully selected and controlled frameworks of reference, by a team of experts with Professor Teuber at its head. For this reason the book contains no compressed summary; such a summary would have been misleading for it would necessarily have isolated the factual observations from the contexts within which they were obtained. For the same reason no section of the monograph has been allowed to stand entirely on its own. On the contrary the various sections have been put together in such a way that none of the facts disclosed are presented in isolation. They appear, rather, as a recurrent, statistically significant pattern against a background of experiments conducted from different standpoints, necessarily arising from opposing theories of brain organization and function. The result is a work of scholarship which must be read from cover to cover. This is no hardship for, excluding appendices, there are only 56 pages of text, written in an admirably clear style.

The following quotations can best serve to demonstrate the value of this monograph: "The evidence provided by our study suggests that sensation of the left hand is more diffusely represented in the contralateral hemisphere than that of the right hand; that sensation of the left hand is frequently affected by lesions of the ipsilateral sensorimotor region; and that the nature of sensory impairment of the left hand is not the same as that of the right hand . . ."

XUM

"In view of the considerations advanced in the preceding paragraphs, we believe that our results cannot easily be dismissed as an artefact of the particular material and methods employed. Nevertheless, we recognize the many pitfalls inherent in the study of clinical cases. It is possible that some less obvious circumstance than those we have considered did introduce bias into our samples. We hope our results will be considered provocative enough to prompt further work, and sufficiently well founded to warrant tentative acceptance until they can be confirmed or denied by investigation of other samples of brain-injured subjects in which accidental factors would presumably be different. . . ."

"If then, we tentatively accept our findings as genuine, their implications for the study of discriminative behaviour, and for the analysis of the disorganizations of discriminative behaviour which may follow brain injury, remain to be considered. Our results suggest that, in man at least, disorders of somato-sensory discriminative function are not likely to be equivalent for right and left hands. The particular hand on which the deficit appears cannot be ignored in consideration of whether and how the deficit can be analysed."

GRAHAM WEDDELL.

Visual Field Defects after Penetrating Missile Wounds of the Brain. By H. L. TEUBER, W. S. BATTERSBY and M. B. BENDER. Pp. 142. Oxford University Press. Price 38s.

Visual field defects were found in 46 of over 200 cases of gunshot wounds of the brain, five to ten years after wounding. These 46 subjects were very extensively studied. The field defects were constant through the years although the patient's total fields varied from time to time in different test situations. The field defects were related to already established anatomical facts; occipital pole injuries caused macular blindness, more anterior cortical lesions macular sparing. The observations of World War I on the nature of small central field defects were confirmed, but interpretation of their shapes calls for revision of the views on the organization of the central visual pathways. The macular fibres in the anterior part of the radiation for instance overlap those serving peripheral vision, and are not central.

Macular sparing may depend on the development of a pseudofovea, on incongruity of field defects or on lower vulnerability of the central fields to damage.

There were many individual anomalies encountered, including frequent incongruity of fields with cortical lesions, and irregularities in the division between seeing and blind fields. The anomalies and unexpected findings in individual cases call for re-evaluation of the theories relating visual perception to their morphological basis, and any theories adopted must take account of these anomalies instead of ignoring them, as in the past.

DENIS WILLIAMS.

SHORTER NOTICES

Nose and Throat Histology—Photomicrographs. By JAMES A. MOORE, M.D. Pp. 64. London: Macmillan. Price 52s. 6d.

This series of photomicrographs of the mucous membrane of the respiratory tract and of the upper digestive tract and associated glands was prepared by Dr. James A. Moore during his residency at the Massachusetts Eye and Ear Infirmary under the late Dr. Harris P. Mosher.

Its chief interest to the neurologist will be in the details of the epithelium lining the various parts of the respiratory tract which is so often responsible for infection spreading to the central nervous system.

TERENCE CAWTHORNE.

The Electrical Activity of the Nervous System. Second edition. By MARY A. B. BRAZIER, Ph.D. Pp. 273. London: Pitman Medical Publishing Co. Price 35s.

Though this is modestly called a textbook for students, it is excellent reading for any neurologist, academic or clinical. From a clear statement of the electrical changes associated with nervous activity in the axon Dr. Brazier goes on to consider the action potentials and the excitability of peripheral nerve. From there to the compound action of nerve tissues and the propagation of the impulse in them, through the synapses, to the cord. There, after rather elementary consideration of the special senses, there are concise essays on the brain-stem, the reticular structures, thalamus and cortex.

The argument is advanced upon pieces of basic research and classical experiments, which are milestones in physiology, and is correspondingly lucid. It is lightened by many illustrations from these classics, and is briefly but well documented.

DENIS WILLIAMS.

Klinische Neuroradiologie. Ed.: Prof. Dr. KURT DECKER. Stuttgart: Georg Thieme Verlag. Price DM 230.

This excellently produced monograph contains 550 illustrations nearly all of superb quality. The team assembled by Professor Decker to produce this monograph on Clinical Radiology, includes Fischgold and Metzger of Paris, Mark and Schunk of Boston, Taveras of New York, McRae of Montreal, and Wiedenmann from Munich.

The whole field of neuroradiology is comprehensively covered in this outstanding work, which will prove invaluable to radiologists, neurosurgeons and neurologists who read German, but even to those who do not the book can be recommended for its illustrations, which virtually provide an atlas of Neuroradiology.

DAVID SUTTON.

Principles of General Neurophysiology Relating to Anæsthesia and Surgery. By BARRY D. WYKE. Pp. 136. London: Butterworths. Price 21s.

This book is a reprint of a section of Frankis Evans "General Anæsthesia." It is an interesting and erudite volume but I feel suffers by removal from its original context.

In this form a mass of valuable facts is presented to the reader but without explaining the experimental data from which they are derived. Further, few conclusions are drawn and the practical instruction is too slight to be of great value.

Monitoring by encephalography has been performed in animals and automatic anæsthesia derived. But anyone conversant with the vagaries of this technique in diagnosis would hesitate to rely too much on its value to the anæsthetist. It is unfortunate that the material must be so condensed as to make it hard reading. There is an excellent bibliography to each section.

ROBERT BEAVER.

A Stereotaxic Atlas of the Dog's Brain. By ROBERT K. S. LIM, M.B., Ph.D., D.Sc., Medical Sciences Research Laboratory, Miles Laboratories, Indiana. CHAN-NAO LIU, Ph.D., Department of Anatomy, University of Pennsylvania. ROBERT L. MOFFITT, B.S., Medical Sciences Research Laboratory, Miles Laboratories, Indiana. Pp. 93. Oxford: Blackwell. Price 74s.

The authors are able to select "short-haired hound-like dogs of limited weight" (10 ± 2 Kg.), and the group on which the data are based comprises 37 mongrels and 5 beagles. The mean and standard deviations are given for the measurements of many intracranial structures from standard planes of reference. This is a well produced and thorough piece of work but unfortunately of very limited application.

JOHN BATES.

XUM

Exploration Du Cerveau Humain par Electrodes Profondes. By MICHEL RIBSTEIN, Electroencephalography and Clinical Neurophysiology, Supplement No. 16. Pp. 129. 30·00 N.F.

In the first section the author gives a full presentation of 7 cases with different varieties of epilepsy who were investigated by the depth electrode technique. He stresses that in some cases an operation was deferred on finding foci of abnormality. The second section comprises a full review of 280 references to the literature. Although the presentation is uncritical, it gives a useful introduction to work which is attempting to increase the clinical value of electrophysiological investigation.

JOHN BATES.

Markhaltige Faserverbindungen am Hirnstamm der Katze. By Prof. SANDRO BURGI and VERENA M. BUCHER. 1960. (Monographien aus dem Gesamtgebiete der Neurologie und Psychiatrie H.87.) Berlin: Springer Verlag.

The book is based on the neurological studies of 75 animals previously stimulated at various points in the brain-stem by W. R. Hess. The sites giving certain responses were coagulated and subsequent Marchi degeneration has been related to the functional results.

Besides integrating anatomy and neurophysiology, the authors fully discuss their subject with related observations of experimental and clinical neurology. This painstaking work deserves full praise and is a valuable guide to both neurologist and neuroanatomist.

PAUL GLEES.

A Polychrome Atlas of the Brain Stem. By W. J. S. KRIEG. Pp. 22. Price $3.00.

Slice Reconstructions of Human Cerebral Sections. By W. J. S. KRIEG. Pp. 25. Price $1.00.

These are paperback collections of large labelled line drawings of the microanatomy of the neuraxis, meticulous in their morphological detail.

NOTICE

COLLEGE OF SPEECH THERAPISTS

THE College of Speech Therapists is holding a Conference in Birmingham from July 24 to 28, 1961.

Abnormalities of speech and language will be presented as systemic disorders under the guidance of the concepts of Signs, Signals and Symbols.

For further information please write to The Conference Organizing Secretary, 16, York Road, Birmingham, 16.